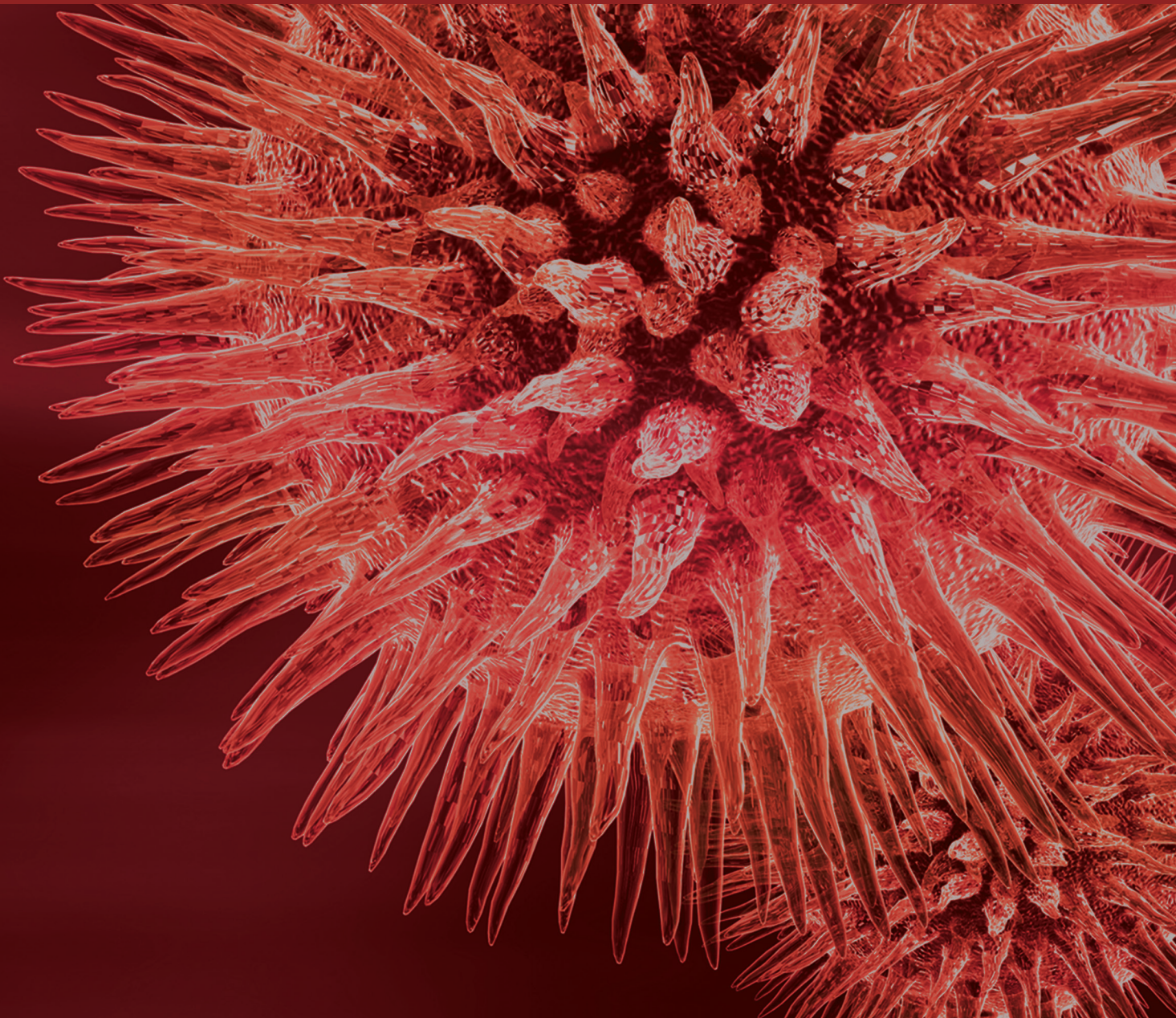


High-Intensity Physical Training in the Treatment of Chronic Diseases and Disorders

Guest Editors: Lars L. Andersen, David G. Behm, Nicola A. Maffiuletti, and Brad J. Schoenfeld





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Editorial

High-Intensity Physical Training in the Treatment of Chronic Diseases and Disorders

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Chronic diseases, such as diabetes, stroke, heart disease, cancer, and chronic respiratory diseases, are the leading cause of mortality worldwide, accounting for two-thirds of all deaths. Musculoskeletal disorders, such as osteoarthritis, rheumatoid arthritis, osteoporosis, neck pain, and low back pain, are associated with disability, loss of productivity at work, and sick leave. Neurological disorders can affect both physical and mental function and lead to major disability and suffering. In recent years, high-intensity physical training, such as high-intensity cardiovascular training or strength training, has become increasingly popular in rehabilitation of many of these chronic diseases and disorders. However, the efficacy and safety of such high-intensity physical training in the prevention and treatment of chronic diseases and disorders still need to be explored.

In this special issue we invited researchers to contribute original research articles as well as review articles investigating the role of high-intensity physical training in the treatment of chronic diseases and disorders. A wide array of topics is discussed in this special issue, including (1) recovery after ACL reconstruction, (2) chronic kidney disease, (3) frail elderly, (4) hypertension, (5) inflammatory bowel disease, (6) degenerative spinocerebellar disease, (7) chronic pain in the neck and shoulders, (8) obesity, (9) cognitive impairment, (10) substance use disorder, and (11) cardiometabolic risk factors.

Our goal was to touch on different aspects of high-intensity physical training in the treatment of chronic diseases and disorders. We are delighted to see the outcome of the special issue and hope that it will inspire and stimulate further research in this area.

Acknowledgment

The editors of this special issue are indebted to all the authors who provided either original data or a comprehensive review of the previous and recent literature, making this special issue appealing to a diverse audience of researchers.

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Review Article

The Role of Physical Exercise in Inflammatory Bowel Disease

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We reviewed and analyzed the relationship between physical exercise and inflammatory bowel disease (IBD) which covers a group of chronic, relapsing, and remitting intestinal disorders including Crohn's disease (CD) and ulcerative colitis. The etiology of IBD likely involves a combination of genetic predisposition and environmental risk factors. Physical training has been suggested to be protective against the onset of IBD, but there are inconsistencies in the findings of the published literature. Hypertrophy of the mesenteric white adipose tissue (mWAT) is recognized as a characteristic feature of CD, but its importance for the perpetuation of onset of this intestinal disease is unknown. Adipocytes synthesize proinflammatory and anti-inflammatory cytokines. Hypertrophy of mWAT could play a role as a barrier to the inflammatory process, but recent data suggest that deregulation of adipokine secretion is involved in the pathogenesis of CD. Adipocytokines and macrophage mediators perpetuate the intestinal inflammatory process, leading to mucosal ulcerations along the mesenteric border, a typical feature of CD. Contracting skeletal muscles release biologically active myokines, known to exert the direct anti-inflammatory effects, and inhibit the release of proinflammatory mediators from visceral fat. Further research is required to confirm these observations and establish exercise regimes for IBD patients.

1. Introduction

Chronic inflammation plays a central role in the pathology of many diseases. For some, such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), and asthma, the most characteristic is a massive infiltration of inflammatory cells at the site of disease activity and the local presence of inflammatory mediators in elevated concentrations as well as their abundance in the systemic circulation. These may lead to pathological disorders in organs distant from the primary inflammatory lesions probably evoked by systemic inflammatory mediators [1].

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of IBD characterized by a cyclic nature, alternating between active and quiescent states impairing

patients' quality of life. Although the inflammatory process in CD is typically transmural and can affect any part of the gastrointestinal tract, the UC affects only the colon and is limited to the mucosa and superficial submucosa [2]. Anorexia, malnutrition, altered body composition, and development of mesenteric white adipose tissue (mWAT) hypertrophy (accumulation of intra-abdominal mWAT) are other well-known features of IBD and especially of CD [2]. Additionally, apart from intestinal changes in CD, the secondary disorders in distant organs such as skin lesion, arthritis, osteoporosis, eye, and liver disorders may frequently occur [2]. Association between inflammation and carcinogenesis is well proven and IBD is an important risk factor for the development of colon cancer [3]. Although progress has been made in understanding the IBD, its etiology is still unknown. The accepted

theory suggests that a combination of environmental agents and a dysfunctional mucosal immune system in genetically susceptible individuals could lead to the development of either CD or UC [4, 5]. It was established that CD is a Th1 cytokine-mediated disease characterized by increased production of interferon (IFN-) γ , whereas UC most likely resembles a modified Th2 profile, characterized by increased production of interleukin- (IL-) 5 production and normal IFN- γ production [6]. Cytokines, such as TNF- α , IL-1 β , and IL-6 are more promiscuous in their function because they are associated with both forms of IBD to a lesser or greater degree [6, 7]. Each of these cytokines can activate NF- κ B and the mitogen-activated protein kinases, thereby initiating a cascade of “downstream” proinflammatory effects that are the immediate prerequisites of tissue and organ pathology in IBD [6]. Recently, TNF-like weak inducer of apoptosis (TWEAK), the TNF super family (TNFSF) member, has appeared as a new factor in the inflammatory processes and its crucial role in IBD has been proposed [8–10]. Its actions are mediated by binding to fibroblast growth factor-inducible 14 (Fn14), surface receptor that has been linked to several intracellular signaling pathways, including the nuclear factor- κ B (NF- κ B) inflammatory pathway [11]. Fn14 can be upregulated on intestinal epithelial cells, most probably by their exposure to microbial or inflammatory products and contribute to failure of the mucosal barrier; the induction of IEC-derived mediators that promote chronic inflammation and shape gut immunity against commensally bacteria [9]. Interestingly, this expression of Fn14 is upregulated in CD patients [11].

The concept of exercise training could cover heterogeneous interventions that differ in type (e.g., endurance versus resistance training, acute versus chronic exercise), intensity, frequency, and duration. Structured exercise training could consist of aerobic exercise, resistance training, or a combination of both. In contrast to structured exercise training, physical activity is defined as any bodily movement produced by skeletal muscle contractions resulting in increased energy expenditure [12].

The well-documented observations that physical activity is inversely correlated with systemic low-level inflammation lead to suggestion that the anti-inflammatory activity induced by regular exercise may be responsible for some beneficial health effects in patients with chronic diseases [13]. However, the intensive exercise may induce a transient mild systemic inflammation and increased level of cytokines and these adverse effects depend on intensity and duration of exercise. Following prolonged and strenuous exercise, the function of the immune system is impaired for several hours [14, 15], but on the other hand, the regular exercise training has been shown to increase resistance to infections [16–19].

The possible beneficial effects of physical activity on the gastrointestinal tract have been so far little studied. It is known that intensive exercise such as long distance running and triathlons could cause nausea, heartburn, diarrhea, or even gastrointestinal bleeding and marathon runners suffer from “runner’s ischemic colitis,” involving bloody diarrhea,

fatigue, and fever [20]. The involvement of physical activity in prevention of colon cancer [21] has been well proven, but the effect of physical activity on IBD is less documented and the importance of exercise as adjunct anti-inflammatory therapy has been suggested [22–24]. There is a general commitment that IBD patients could benefit from physical training because regular exercise could improve psychological health and reduce some disease symptoms and complications [25]. However, from our current knowledge on exercise in relation to immune functions, cytokines network, and in particular, the secretory role of contracting muscles, one concludes that a relatively small attention has been addressed to mechanisms of action of regular exercise in patients with a chronic inflammatory disease like IBD, in which immune response is impaired. Most studies have examined the beneficial effects of exercise in terms of quality of life and general fitness but relatively few studied effects of training on disease pathogenesis and measures of inflammation and evidence-based recommendations could not yet be made for this disease [22–25].

Taking into the account the lack of sufficient evidence-based exercise guidelines for those subjects who suffer from IBD and that physical activity is recommended for such patients as a complementary medical therapy, the purpose of the review was to evaluate published human and experimental research studies focusing on physical activity and IBD.

Particular aims of the present review were to update the literature on physical activity in IBD and to evaluate (1) whether physical activity in the preillness period could influence onset of IBD, (2) impact of exercise on IBD, and (3) overview on selection of types and intensities of exercise in individuals suffering from this disease and how exercise affects experimental models of this disease. In discussion, we focused on potential mechanisms of beneficial action of physical training.

2. Methods

2.1. Search Strategy. We searched the following electronic databases up to January 2014: MEDLINE (accessed by PubMed), Google Scholar, Web of Science, PEDRo, and IBD/FBD Group Specialized Register (June 2013). The following search string was entered into each database using MeSH terms, appropriate alternatives, and Boolean operators: inflammatory bowel disease, Crohn’s disease, or ulcerative colitis and exercise, physical activity, physical fitness, or physical training. Variations of the above search strategy were used to search the databases other than Medline.

2.2. Study Selection. Two reviewers (JB and TB) independently assessed study eligibility and the full-text articles were then examined. Bibliographies from existing articles were screened manually. Only fully published papers were reviewed. Figure 1 provides a flowchart of study selection. In Figure 2, the insight into mechanism of crosstalk between skeletal muscle, adipose tissue and the inflammation in the gut is presented.

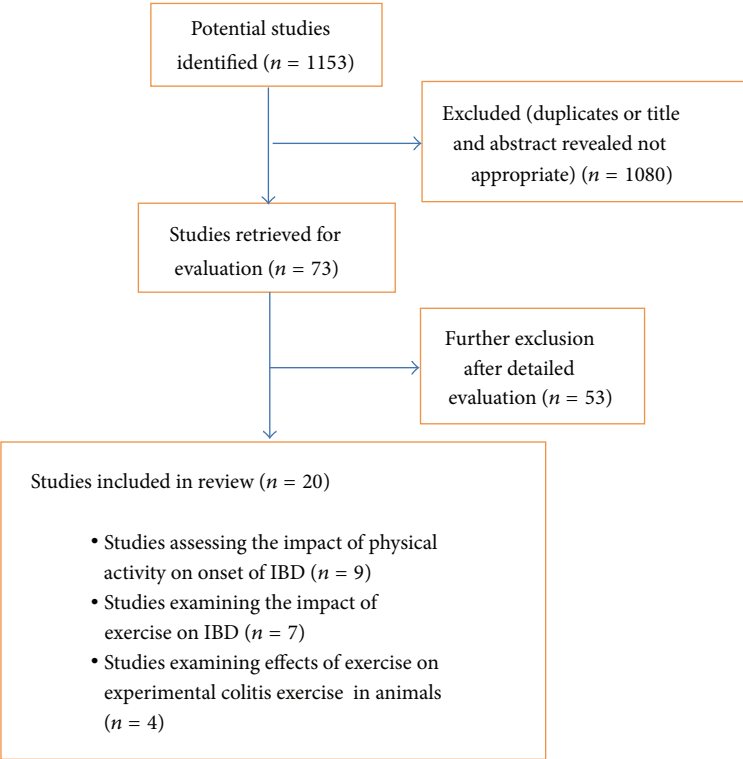


FIGURE 1: Flowchart for selection of studies.

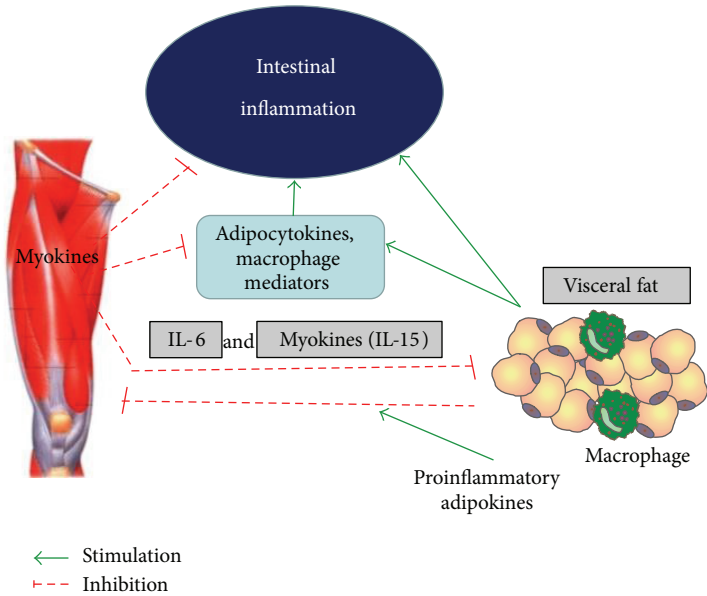


FIGURE 2: Crosstalk between skeletal muscle, adipose tissue, and intestinal inflammation.

3. Results

3.1. Exercise in the Preillness Period. The incidence and prevalence of IBD rapidly increased in last years in developed countries and the rise witnessed in the rest of the world closely correlates with adopting a western lifestyle [26].

These observations support the notion that a variety of environmental factors contribute to the pathogenesis of intestinal diseases [26]. In developed countries, peoples’ lifestyle has changed significantly, being affected by serious modifications in dietary habits and physical inactivity [27]. Those changes in lifestyle may have a bearing on the course of the disease. Some

TABLE 1: Characteristics of studies assessing the impact of physical activity on onset of IBD included in review.

Reference	Number of subjects	Study characteristics	Study outcome
Sonnenberg, 1990 [28]	12 014	Retrospective study (Germany)	Occupations characterized by outdoor physical work appeared to be protective compared with those occupations classified as sedentary against the onset of IBD
Persson et al., 1993 [29]	152 CD 145 UC 305 controls	Postal questionnaire (Sweden, Stockholm County)	CD onset (but not UC) inversely related to weekly and daily exercise five years before disease onset
Boggild et al., 1996 [30]	2 273 872	A cohort, comprising male and female aged 20–59 (January 1986), was followed up for hospitalizations due to chronic IBD until December 31, 1990 (Denmark)	Sedentary office work may contribute to IBD onset
Klein et al., 1998 [31]	55 UC 33 with CD 76 population and 68 clinic controls	Preillness lifestyle patterns compared among recently diagnosed IBD patients and matched population and clinic controls (Israel)	IBD patients had lower levels of physical activity during their preillness period compared to clinic but not population controls
Cucino and Sonnenberg, 2001 [32]	2399 CD and 2419 UC	Examined the occupations of IBD mortalities 1991–1996 (USA)	IBD mortality was low in occupations associated with manual work and relatively high in sedentary occupations in both CD and UC
Halfvarson et al., 2006 [33]	Discordant twin pairs 102 CD 125 UC	Population-based twin cohort using the cotwin control method through a postal questionnaire (Sweden, Denmark)	No significant difference found in physical activity between twins pairs
Chan et al., 2013 [34]	300 724	Anthropometric measurements of height and weight plus physical activity and total energy intake from validated questionnaires taken at recruitment. The cohort was monitored identifying participants who developed either CD or UC (European Prospective Investigation into Cancer and Nutrition study.).	No association was found between physical activity and onset of IBD
Hlavaty et al., 2013 [35]	190 CD 148 UC 355 controls	Case-control study through questionnaire (Slovakia)	CD and UC associated with less than two sporting weekly activities
Khalili et al., 2013 [36]	194 and 711 women	Women enrolled in this prospective cohort study provided data on physical activity since 1984 in the Nurses' Health Study and 1989 in the Nurses' Health Study II and followed up through 2010 (USA).	Physical activity was inversely associated with risk of Crohn's disease but not of ulcerative colitis

studies have examined the effect of lifestyle and particularly physical activity as supposed by causal agents for the onset of IBD (Table 1).

The protective role of physical activity against the onset of IBD was first postulated by Sonnenberg [28] who found that occupations characterized by outdoor physical work appeared to be protective compared with those occupations classified as sedentary in retrospective study in male and female German workers. In small ($n = 725$) case-control study Persson et al. [29] reported an inverse association between physical activity and CD (but not UC) onset in a Swedish cohort. A prospective study which followed two cohorts, each of more than 2.3 million persons in Denmark,

for 5 or 10 years, found a small association between sedentary office work lifestyle and the onset of IBD [30]. In 1998, a study by Klein et al. [31] determined that IBD patients ($n = 88$) had lower levels of physical activity during their preillness period than clinic controls ($n = 68$; $P < 0.001$). IBD patients had lower levels of physical activity during their preillness period compared to clinic but not population controls. Cucino and Sonnenberg [32] examined the occupations of IBD mortalities between 1991 and 1996 in 2399 CD and 2419 UC patients in USA and found that IBD mortality was low in occupations associated with manual work and relatively high in sedentary occupations. When Halfvarson et al. [33] studied environmental factors in a population-based Swedish-Danish

TABLE 2: Characteristics of interventional studies examining the impact of exercise on IBD.

Reference	Sample	Disease type	Intervention	Duration of exercise program	Outcome
Robinson et al., 1998 [122]	117 patients: 60 exercise 57 control	CD	Home based low impact exercises program of increasing intensity focused on the hip and lumbar regions	Twice a week (at least 10 monthly), 12 months	Bone mineral density increased in compliant patients in the lumbar spine and the hip
D'Inca et al., 1999 [42]	6 patients in remission 6 control	CD	Acute exercise at 60% of VO_{2max} (cycle ergometer)	One hour	Exercise did not elicit subjective symptoms or changes in intestinal permeability and lipid peroxidation
Loudon et al., 1999 [38]	12 patients with inactive or mildly active disease	CD	Low-intensity walking program subjects walked an average of 2.9 sessions/wk, at an average of 32.6 min/session, and for an average distance of 3.5 km/session	A thrice weekly, 12 wk walking program	Stress diminished, physical health, general well-being, and quality of life improved without disease exacerbation
Elsenbruch et al., 2005 [139]	30 patients with inactive disease 30 control	UC	60 h training program: stress management program, light exercise	10 weeks; 6 h/week	Improvement in quality of life in patients with UC in remission, while no effects of therapy on clinical or physiological parameters were found
Ng et al., 2007 [39]	16 patients with inactive disease 16 patients control	CD	Low-intensity walking 30 min at 60% of maximum heart rate	3 times per week during 3 months	Improvement in quality of life and reductions in CD symptoms
Ploeger et al., 2012 [44]	15 pediatric patients in remission 15 controls	CD	Moderate intensity continuous exercise (MICE) High intensity intermittent exercise (HIIE)	30 min of cycling at 50% of peak mechanical power (PMP) 6 bouts of 4 × 15-s of cycling at 100% PMP	No significant exacerbation of the disease or inflammatory cytokine responses in both types of exercise
Chan et al., 2014 [45]	918 IBD patients (54% CD and 46% UC)	CD, UC	UK online survey regarding exercise habits	Regular exercise	72% reported that exercise made them feel better, but 80% had to stop exercising temporarily or permanently at some point because of the severity of their symptoms

twin cohort using the cotwin control method, they found no significant differences between the twins in physical activity before the diagnosis of IBD.

In a recent the European Prospective Investigation into Cancer and Nutrition study, 300,724 participants were recruited into and the cohort was monitored identifying participants who developed CD or UC, but physical activity did not show any association with UC or CD [34]. In case-control study in Slovakia [35] which included 338 patients (190 CD, 148 UC) and 355 controls CD and UC, an onset of IBD was inversely associated with physical activity. In another recent study in two large prospective cohorts of US women (194 711 women) the association between physical activity and risk of ulcerative colitis and Crohn's disease was studied [36]. Women enrolled in this prospective cohort study provided

data on physical activity since 1984 in Nurses' Health Study and 1989 in Nurses' Health Study II and followed up through 2010 (USA). Physical activity was found inversely associated with risk of Crohn's disease but not of ulcerative colitis.

The physical activity in preillness period was shown to reduce risk of the onset of IBD and this reduction was found to be stronger for CD than UC [29, 36].

3.2. Impact of Exercise on IBD. The physical activity has been used in IBD as an adjunctive therapy regime, although the effectiveness of exercise on disease activity has not been well described and the mechanisms of its potential beneficial effects are poorly understood [25, 37]. Studies that examined the effect of exercise on IBD involved mainly patients with quiescent state of disease (Table 2). In sedentary patients with

inactive or mildly active CD, the moderate exercise by means of walking program or yoga led to significant improvement in measures of quality of life and stress levels [38–41]. The moderate-intensity exercise was well tolerated by IBD patients who are in remission and did not provoke subjective symptoms or changes in gastrointestinal parameters [42, 43]. Ploeger et al. [44] tested the effect of moderate intensity continuous exercise and high intensity intermittent exercise in youth with CD and concluded that such patients can engage in different types of exercise without a significant exacerbation of the disease. The results of the UK online survey have shown that a majority of respondents were undertaking regular exercise which was found to be beneficial for the symptoms of IBD. However, most of the respondents were prone to stop exercising at some point because of their increased incidents of complaints on severity of symptoms [45].

3.3. Intestinal Disorders and Physical Activity in Experimental Animals. Some of these aspects were also observed at experimental conditions because in mouse model of colitis, the forced treadmill exercise training exacerbated inflammation and increased mortality, while voluntary wheel training was protective in this rodent model [46]. This effect of treadmill exercise was accompanied by increased morbidity due to excessive diarrhea episodes and mortality [46]. In contrast, thirty days of voluntary wheel running attenuated inflammatory gene expression in the distal colon reduced the diarrhea incidences and protected mice from colitis-induced morbidity [42]. Moreover, the induction of experimental colitis by TNBS or dextran sulfide administration caused a significant increase in the TNF-content in the colonic mucosa and submucosa [47, 48]. In another study, the long-term physical exercise of 6-week running attenuated the colonic TNF- α protein content indicating an anti-inflammatory impact of exercise training [49]. Some studies have shown that both forced treadmill and voluntary wheel exercise training can exert an anti-inflammatory effect in the inflamed colon [48–51]. In study by Saxena et al. [48] exercise training (treadmill running at gradually increasing speeds 10, 12, 16, and 18 m/min and a 5% incline for 20 min) significantly decreased proinflammatory cytokines in the adiponectin knockout mice with dextran sodium sulfate induced experimental colitis. In another study moderate exercise (30 min per day of swimming) attenuated chronic stress-induced intestinal barrier dysfunction in mice, possibly due to augmentation of antimicrobial responses in the small intestine [52]. A summary of experimental studies on the experimental IBD and exercise depending on its intensity is shown in Table 3.

4. Discussion

These findings point to the important role for exercise in the adjunct treatment of IBD in humans. Since IBD affects up to 0.25% of the US population or ~750,000 people; thus it is considered as a significant problem [53]. The fact that selection of a proper dosage of the exercise was able to alleviate colitis symptoms, reduce colon inflammation, and counteract the

adverse effects associated with pharmacological therapy (e.g., 5-aminosalicylic acid) [47–49] seems to be of key interest in convincing medical professionals to adopt the life style strategy as an adjunct therapy in their IBD treatment.

The protective effect of exercise may to some extent be attributed to its anti-inflammatory effect and it may mediate via muscle-derived peptides, the so-called “myokines” [54]. Contracting skeletal muscles release myokines like IL-15 with endocrine effects, mediating direct anti-inflammatory effects, and/or specific effects on visceral fat [54]. Possible role of a new myokine irisin which is released during exercise and act on the white fat cells is still studied [54].

Creeping fat in patients with Crohn’s disease refers to hypertrophy of the mesenteric fat tissue located around the inflamed parts of the intestine [55] and recent research suggests that this fat wrapping contribute actively to disease severity and may influence onset of complications [56–63]. Accumulating evidence suggests that mesenteric white adipose tissue (mWAT), composed of not only fat but also macrophages and T lymphocytes, plays an important role as the source of inflammation and releases various inflammatory factors such as cytokines and chemokines [64–68]. This mesenteric fat which is present from the onset of disease is associated with overexpression of TNF- α , leptin, and other adipokines and correlates with the severity of intestinal inflammation and tissue injury, suggesting an important role for adipose tissue in the intestinal inflammatory process in CD [55, 62, 69–71]. The intestinal luminal leptin, a cytokine produced by adipocytes, is increased in CD and can upregulate NF- κ B expression in colonic epithelial cells [58, 72–74]. Leptin is considered to be a proinflammatory cytokine [58] and directly regulates production of several cytokines, particularly those released from T cells. It increases IL-2 and interferon γ production while decreasing IL-4 levels [58]. An overexpression of leptin mRNA in mWAT was reported in IBD patients, indicating that leptin might participate in the inflammatory process by enhancing mesenteric TNF- α expression [75, 76] and leptin levels have been shown to be significantly higher in mesenteric adipose tissue from CD patients, than in patients with noninflammatory disease [58, 72]. Experimental colitis in rats resulted in elevated circulating leptin levels which correlate with the degree of inflammation and the development of anorexia [77] and leptin antagonist ameliorated the development of chronic experimental colitis [78]. Another adipokine, adiponectin, which is considered anti-inflammatory, has a structure similar to TNF- α but antagonizes its effects by reducing secretion and attenuating the biological actions by competing for the receptor [79–81]. Divergent data have been presented about circulating levels of adiponectin in patients with IBD [72, 74, 80, 82–86]. Adiponectin production is enhanced in hypertrophied mWAT which remained in contact with the intestine of CD patients, and this increase may be specifically related to inflammation and the presence of this fat wrapping [79, 87]. A role for hypertrophied mesenteric fat tissue as a barrier to the inflammatory process was postulated in other studies [86, 88, 89]. However, recent observations of lower levels of serum and mesenteric adiponectin in active CD patients compared with those in remission suggest a

TABLE 3: Characteristics of animal studies examining effects of exercise on experimental colitis.

Reference	Species	Study characteristics	Study outcome
Cook et al., 2013 [46]	Male C57Bl/6J mice	Mice were randomly assigned to 3 groups: (1) sedentary, (2) moderate intensity forced treadmill exercise (FTR) (8–12 m/min, 40 min, 6 weeks, and 5x/week), or (3) voluntary wheel training (VWR) (30 days access to wheels). Dextran sodium sulfate (DSS) was given at 2% (w/v) in drinking water over 5 days. Mice discontinued exercise 24 h prior to DSS treatment.	Forced treadmill exercise exacerbated the colitis manifestation and mucosal inflammation (rise in diarrhea and gene expression of IL-6, IL-1 β , and IL-17 in the colon. Also higher mortality was observed in the FTR/DSS group. VWR alleviated colitis symptoms and reduced inflammatory gene expression in the colonic mucosa of DSS-treated mice.
Saxena et al., 2012 [48]	Male adiponectin knockout (APNKO) and wild type (WT) mice (C57BL/6)	APNKO and WT mice were randomly assigned to different groups: (1) sedentary (SED); (2) exercise trained (ET); (3) sedentary with dextran sodium sulfate (DSS) treatment (SED + DSS); and (4) exercise trained with DSS (ET + DSS). Exercise-trained mice ran at 18 m/min for 60 min, 5 d/wk for 4 weeks. Subsequently, the ET + DSS and the SED + DSS mice received 2% DSS in their drinking water for 5 days (d), followed by 5 d of regular water.	The clinical symptoms of colitis were unaffected by exercise and there was no difference between the APNKO and WT mice. The clinical symptoms of the DSS-treated APNKO mice were worse than WT mice treated with DSS and had increased local STAT3 activation, higher IL-6, TNF- α , IL-1 β , and IL-10. Exercise training significantly decreased proinflammatory cytokines including IL-6, TNF- α , and IL-1 β and the phosphorylation expression of STAT3 in both WT and APNKO mice in DSS + EX.
Hoffman-Goetz et al., 2010 [49]	Female C57BL/6 mice	Animals were given 16 weeks of wheel running (WR) or a control condition and at the end of training were assigned to a single acute treadmill exercise session (30 min at 22 m/min, 30 min at 25 m/min, and 30 min at 28 m/min).	WR mice had lower TNF- α and caspase 7 and higher IL-10 and IL-6 expression in intestinal lymphocyte (ILymph) than No WR mice. A single exposure to intense aerobic treadmill exercise increased pro-(TNF- α) and anti-(IL-10) inflammatory cytokine and proapoptotic protein (caspase 3) expression in ILymph. The percent of early and late apoptotic and dead ILymph were higher after acute exercise.
Luo et al., (2013) [52]	Male Balb/c mice	Effect of moderate exercise (30 min per day swimming) on repeated restraint stress-(RRS-) induced intestinal barrier dysfunction.	Exercise attenuated chronic stress-induced intestinal barrier dysfunction in mice, possibly due to augmentation of antimicrobial responses in the small intestine.

defective regulation of anti-inflammatory pathways in CD pathogenesis [80]. The impaired balance between proinflammatory and anti-inflammatory factors due to an increase in secretion of TNF- α , leptin, and the release of chemoattractant protein-1 (MCP-1) and the decreased production of adiponectin could result in macrophage accumulation in adipocytes and an inflammatory transformation of the visceral adipose tissue, leading to the appearance of creeping fat [88]. Adipocytokines and macrophage mediators secreted by the creeping fat could further increase the intestinal inflammatory process, leading to mucosal ulcerations along the mesenteric border, a typical feature of CD [82, 90]. The massive cytokine production in the inflamed colon, in addition to translocating bacteria, could further induce the production of proinflammatory mediators in the adjacent adipose tissue, thus inducing a vicious cycle, in which inflammatory conditions in the intestine and the mesenteric fat support each other [88, 91]. Cytokine overproduction and

particularly leptin by mesenteric fat could lead to anorexia, another feature present in CD [86].

4.1. Importance of Skeletal Muscle Crosstalk with the Fat Tissue and the Gut in Protection against Intestinal Disorders. Exercise could improve nutrient metabolism in skeletal muscle as well as vascular function and microcirculation, but the accumulated so far evidence suggests that the protective effect of exercise may to some extent be ascribed to its anti-inflammatory effect. Exercise may exert its anti-inflammatory effect via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise. Such effects may in part be mediated via muscle-derived peptides [54]. If the endocrine and paracrine functions of the muscle are not stimulated through contractions, this will cause dysfunction of several organs and tissues of the body as well as an increased risk of chronic inflammatory diseases [54, 92, 93]. As mentioned before, myokines may

balance and counteract the effects of adipokines taking part in crosstalk between skeletal muscle and adipose tissue [37, 54]. The secreted myokines are associated with muscle function revealing a novel secretory proteins released from skeletal muscles during exercise that also have been shown to be impaired with ageing.

The prototype myokine, IL-6, appears to be able to mediate metabolic effects as well as anti-inflammatory effects. In response to muscle contractions muscle fibres express the myokine IL-6, which exerts its effects both locally within the muscle and in several distant organs [54, 94]. It has been accepted that the rise in IL-6 level was a consequence of immune response to local damage observed during exercise. Nowadays it is known that muscle is unique in its ability to produce IL-6 during contraction in completely TGF-independent mode. This suggests a major role for this cytokine in a regulation of metabolism rather than acting as an inflammatory mediator [95, 96]. It was shown that IL-6 released by muscle during exercise can mediate release of GLP-1 from intestinal L cells (and from pancreatic A cells) which in turn acts as an incretin causing insulin release providing an evidence that there is possible crosstalk between adipocytes, muscle, and pancreas responsible for energy homeostasis [96]. The exercise increased dramatically level of IL-6 in mice and induced a parallel marked rise in GLP-1 [96]. Glucagon-like peptides are trophic growth factors that enhance repair of damaged intestinal mucosa and the release of these factors could be in part responsible for beneficial effect of exercise [97–100].

IL-15 that is expressed in human skeletal muscle has been identified as an anabolic factor in muscle growth and has been implicated in muscle-fat crosstalk [54]. It was demonstrated that IL-15 mRNA levels were upregulated in human skeletal muscle following a bout of strength training, suggesting that IL-15 may accumulate within the muscle as a consequence of regular training [101]. Interestingly, a decrease in visceral fat mass, but not subcutaneous fat mass, was observed, when IL-15 was overexpressed in murine muscle. Also the elevated circulating levels of IL-15 resulted in significant reductions in body fat and increased bone mineral content [102, 103]. In a recent study, Boström and colleagues [104] identified a new myokine which they called irisin. This myokine is released during exercise and cause the transformation of white fat cells into bright cells (brown-in-white fat cells), with a phenotype similar to that of brown fat cells [104, 105]. In humans, plasma levels of irisin after 10 weeks of regular endurance training were significantly and markedly increased. It was suggested that irisin could be therapeutic for human metabolic disease, obesity, and other disorders in which the exercise is beneficial [104, 105]. Recently, a new myokine secreted protein acidic and rich in cysteine (SPARC) was functionally characterized [93]. SPARC had increased in skeletal muscle and had been secreted into the circulation in response to exercise. The release of SPARC was linked with inhibition of colon tumorigenesis by increasing apoptosis [106]. SPARC is a secreted matricellular glycoprotein that is involved in the development, remodeling, and tissue repair by modulating cell-cell and cell-matrix interactions as well as other functions such as antitumorigenesis action [106].

Interestingly, a single bout of exercise rapidly increased SPARC blood plasma and muscle levels suggesting that the muscle cells secrete this myokine into the circulation. This exercise-induced increase in SPARC appeared to be muscle-specific because no increase was observed in other organs where SPARC was found to be abundant [106].

Depletion of skeletal muscle mass, decreased muscle strength and endurance, and reduced height velocity in children are characteristic features in IBD [2, 107–109]. Particularly in CD, muscle mass and function are reduced compared to healthy controls, potentially resulting in disability [110]. Mechanisms contributing to muscle impairment and thus potential therapeutic targets are poorly understood. The IBD-related growth failure and decreased muscle mass could be the result of a variety of mechanisms including decreased nutrient intake, malabsorption of ingested nutrients, and increased metabolic rate but also could be attributed to elevated concentrations of inflammatory cytokines, decreased level of insulin-like growth factor 1 (IGF-1), and treatment with corticosteroids [111]. Both plasma IGF-I and muscle IGF-I are decreased in response to diverse inflammatory insults that accelerate the loss of muscle protein [112]. The function of the GH-insulin-like growth factor- (IGF-) I axis depends on finely tuned mechanisms, which can be impaired by inflammatory cytokines released from pathologically modified mWAT. Inflammatory cytokines, notably TNF- α , reduce liver GH receptor numbers and seem to be responsible for hepatic GH resistance and decrease of circulating IGF-I level that leads to growth inhibition and decrease of lean body mass (LBM) [112–114]. Recent study has shown an attenuated muscle hypertrophy pathway in CD compared with controls particularly in human subjects with lower serum vitamin D₃ and lower physical activity indices. This reduced muscle mass in CD may be explained, in part, by impaired activation of muscle protein synthesis pathways, in particular IGF1-Akt pathway. Finally, it was concluded that the normal vitamin D levels and regular exercise may be protective in CD [110]. Studies performed on rats with experimental colitis have demonstrated inhibitory effects of inflammation on IGF-I generation and the linear growth, the mechanisms independent of malnutrition [115, 116]. Impaired function of satellite cells is another link between impaired insulin/IGF-I signaling and muscle protein loss [115]. It was shown that resistance training can prevent and even reverse the progression of sarcopenia [117].

Accumulating evidence suggests that peroxisome proliferator-activated receptor γ coactivator α (PGC-1 α) and TWEAK-Fn14 system are key regulators of skeletal muscle mass in various catabolic states. While the activation of TWEAK-Fn14 signaling causes muscle wasting, PGC-1 α preserves skeletal muscle mass. Inflammatory reactions during IBD favor TWEAK-Fn14 system when physical exercise possibly exhibits a counteractive effect [9, 10, 118, 119].

4.2. Other Benefits of Exercise for IBD Patients. Beside the anti-inflammatory actions, several other benefits of physical exercise in IBD patients have been suggested. Ankylosing spondylitis has been specifically associated with IBD, but

the exercise therapy improved the flexibility strength and reduced pain of the joints [120]. IBD is associated with decreased bone mineral density and increased risk of osteoporosis [121] and preventive role of exercise has been proposed [122–124]. It was demonstrated that physical exercise can increase bone mineral density (BMD) in CD and may reduce the risk of osteoporotic fracture [122]. The pediatric patients, particularly with Crohn's disease, are at risk for extra intestinal manifestation including growth failure, weight loss, and anemia. Additional beneficial effect of exercise could be amelioration of accompanying anorexia, possibly by modification of the release of adipokines and ghrelin [125]. The reduced food intake in IBD could be caused by abdominal pain, diarrhea and incontinence, surgery, nausea, depression, or a feeling of general unwellness but satiety control in IBD patients is also probably modulated by availability of inflammatory cytokines like leptin which suppresses appetite, reducing the motivation to eat [126–128]. The fatigue is a commonly observed symptom in CD, even in quiescent state of the disease and this effect is probably mediated, at least in part, by cytokines [93, 129]. Role of exercise in reduction of fatigue in chronic diseases including IBD was emphasized [93, 129, 130]. IBD patients have higher levels of daily stress and a lower quality of life compared with general population but also with those patients who suffer from other chronic diseases [27, 28]. The beneficial role of exercise in such cases has been proven [131, 132].

The effect of exercise on different immune parameters could depend on its intensity, duration, and the type of exercise (e.g., endurance versus resistance training, acute versus chronic exercise). Systematic exercise may be beneficial for CD patients for its anti-inflammatory and anabolic properties. However, acute, strenuous exercise could lead to release of inflammatory cytokines that could be involved in the pathology of CD and even induce an exacerbated inflammatory response [24].

Previous studies show that low-intensity exercise is well tolerated in IBD patients. Moreover, this exerted a beneficial effect on course of this disease. In guidelines created in 1998 specifically for IBD patients, physical exercise was recommended for general health to counteract muscle wasting and improve bone density [133]. An aerobic activity for 20 min to 60 min two to five days every week, accompanied by resistance exercise at least twice per week was recommended. The guidelines, however, were not based on actual research. In recent review authors proposed similar recommendations and suggested that two main types of physical interventions should be recommended for CD patients, namely, the aerobic activity and the muscular resistance training [23].

4.3. High-Intensity Physical Training in the Treatment of IBD. Single bouts of exercise could activate the same inflammatory mediators as those involved in pathology of IBD. It is generally accepted that high intensity exercise may lead to an acute although transient, exacerbation of inflammation, and the symptoms of IBD. Therefore, such training is generally not recommended for IBD patients [24]. However, such recommendations are not well supported by research studies.

Only one study which examined the effect of high intensity intermittent exercise in pediatric patients concluded that that such intense exercise is well tolerated [44].

The generally accepted model for exercise prescription in many chronic inflammatory diseases was moderate-intensity-aerobic continuous training with such proven benefits like increase in exercise capacity, the amelioration of stress, and an increase in quality of life. Recently, however, a body of evidence has indicated that high intensity interval training can be performed safely and lead to similar health effects compared to longer, continuous exercise and is less associated with release of inflammatory mediators [134, 135]. Such exercise program may be particularly beneficial for children with CD, not only to improve exercise capacity, but also because of anabolic action and stimulation of growth and development [136, 137]. On the other hand moderate intensity exercise could be more effective than high intensity in stimulation of release of myokines as shown by Yeo et al. [138].

5. Conclusion

Although anti-inflammatory pharmaceutical treatments are beneficial in reducing IBD symptoms, they are often related to serious side effects and their efficacy is not complete. IBD patients continue to have physical and psychological complaints, impairing their quality of life. Preliminary studies demonstrate that moderate exercise has no negative health effects and may diminish some symptoms of IBD. The exercise is recommended also because it could counteract some IBD specific complications by improving immunological response, psychological health, nutritional status, bone mineral density and reversing the decrease of muscle mass and strength. Recent research suggests that the beneficial effects of regular exercise may be in part due to the anti-inflammatory effects of myokines released due to skeletal muscle contractions. Further studies are definitely required to confirm these observations and establish exercise regimes for different IBD patient groups. Additional basic and clinical research with exercise of higher intensities is also needed to establish a potential acceptable limit for physical activity in IBD patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Motor Training in Degenerative Spinocerebellar Disease: Ataxia-Specific Improvements by Intensive Physiotherapy and Exergames

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The cerebellum is essentially involved in movement control and plays a critical role in motor learning. It has remained controversial whether patients with degenerative cerebellar disease benefit from high-intensity coordinative training. Moreover, it remains unclear by which training methods and mechanisms these patients might improve their motor performance. Here, we review evidence from different high-intensity training studies in patients with degenerative spinocerebellar disease. These studies demonstrate that high-intensity coordinative training might lead to a significant benefit in patients with degenerative ataxia. This training might be based either on physiotherapy or on whole-body controlled videogames (“exergames”). The benefit shown in these studies is equal to regaining one or more years of natural disease progression. In addition, first case studies indicate that even subjects with advanced neurodegeneration might benefit from such training programs. For both types of training, the observed clinical improvements are paralleled by recoveries in ataxia-specific dysfunctions (e.g., multijoint coordination and dynamic stability). Importantly, for both types of training, the retention of the effects seems to depend on the frequency and continuity of training. Based on these studies, we here present preliminary recommendations for clinical practice, and articulate open questions that might guide future studies on neurorehabilitation in degenerative spinocerebellar disease.

1. Introduction

The cerebellum is essentially involved in control of various kinds of motor behaviour such as speech, eye movements, limb movements, and balance. Here, its main function is the shaping and fine-tuning of movements. Correspondingly, cerebellar damage does not lead to reduced or paretic movements but to increased variability and poor accuracy of movements (“ataxia”) [1–3]. For example, ataxic gait is characterized by deficits like disordered coordination between head, trunk, and legs and impaired predictive postural adjustments, for example, impaired predictive postural adjustments

[4] in balance control and multijoint leg coordination [5]. These deficits present as increased step width, variable foot placement, irregular foot trajectories, and a resulting instable stumbling walking path with very high movement variability [6–8] and a high risk of falling [9].

Given the fact that drug interventions are rare in degenerative diseases and limited to only specific type of diseases and symptoms [10], physiotherapy is a major cornerstone in current therapy of ataxic gait. However, while motor training programs have been shown to be beneficial in other neurodegenerative diseases (e.g., Parkinson’s disease or stroke [11, 12]), their effectiveness remains controversial in the field

of degenerative spinocerebellar ataxias [13–15]. Degenerative ataxias indeed seem to be the most difficult group of ataxias to treat. Here, motor training is not only challenged by the fact that the cerebellum is crucially involved in motor adaptation and motor learning [16–19] but is also challenged by the progressive nature of this type of disease and, in addition, by the fact that virtually all parts of the cerebellum are affected (although degeneration is frequently most prominent in the midline [20]). Moreover, degeneration in degenerative ataxias is mostly not limited to the cerebellum but often affects spinocerebellar pathways and dorsal columns as well [21]. In contrast, ataxia following stroke, neurosurgery, or trauma usually affects only circumscribed regions of the cerebellum but leaves other regions intact. These regions may compensate for the defective parts. In addition, in case of focal lesions, effects of neural plasticity are likely more effective because there is no competition with ongoing progressive neurodegeneration [22, 23]. Moreover, whereas patients with focal lesions clearly improve in motor functions over time [24], patients with degeneration slowly deteriorate [25]. Thus, in patients with progressive degenerative diseases, it would be a major achievement if they remained stable on the current status of motor function as long as possible or if progression of functional impairment was slowed down.

Until recently, only relatively few and small clinical studies have evaluated training interventions for patients with spinocerebellar ataxia. Using increasingly demanding balance and gait tasks, improvements were achieved in terms of increased postural stability and reduced dependency on walking aids [26, 27]. Locomotion training on treadmills with [28, 29] or without [30] body-weight support has been proposed, in particular for patients with more severe ataxia, which are not able to walk freely. However, many of these studies were single cases or based on a very small number of patients and did not focus on degenerative spinocerebellar ataxias but on nondegenerative secondary ataxias.

In clinical practice, this problem is complicated by the fact that not only the basis of scientific evidence for physiotherapy is sparse, but also the ataxia-specific expertise among physiotherapists. A large share of physiotherapists reports lack of ataxia-specific expertise and expresses the need for education and evidence-based guidelines [31, 32].

Here, we provide an analysis of the first recent clinical studies which have systematically investigated different training programs in sizeable cohorts of patients with degenerative cerebellar disease. Corroborated by encouraging findings from animal studies, which demonstrated motor learning effects in mice with degenerative cerebellar disease even on a molecular level [33], these studies provide the first systematic evidence for effectiveness of motor rehabilitation in this condition in humans [34–36]. Here, we review their findings, pinpoint their crucial advances and limitations, present recommendations for clinical practice, and articulate new research questions that might guide the field within the next years. This focused review might also facilitate first steps towards the development of evidence-based recommendations and specific education for physiotherapists.

2. Methods

Search Strategy. A selective, focused search was performed by the authors in the electronic databases of PubMed, Medline, and EMBASE. These databases were deemed most likely to cover all relevant clinical trials in this field and in particular to contain all studies that meet the stringent inclusion criteria mentioned below. Clinical trials were identified using a combination of the following terms and MeSH terms: cerebellar ataxia, ataxia, physiotherapy, physical therapy, training, exercise, and rehabilitation. The selected time period was from January 1, 1980, to December 18, 2013, and the articles had to be published in English. The retrieved articles were examined for useful references.

Selection. Articles were included if they met all of the following criteria: (i) original report, but not, for example, conference abstracts or reviews; (ii) prospective clinical trial evaluating the effectiveness of physical therapy or of other motor training programs focusing on gait and stance (e.g., computer assisted training, treadmill training, or videogame based training); (iii) high-intensity training over an extended time period, defined as repeated continuous exercises without interruption for at least >45 minutes per training session with ≥ 3 training sessions and ≥ 3 hours per week for ≥ 2 weeks; (iv) control design (case-control or intraindividual control design), but not uncontrolled case or cohort studies; (v) recruitment of patients with spinocerebellar degeneration, but not with secondary cerebellar ataxias due to, for example, stroke, tumor, trauma, inflammatory, or autoimmune causes (for a systematic review on training studies in these patients; see [37]). Spinocerebellar degeneration had to be a core feature in these patients. Studies were also included if degeneration of additional tracts was present, for example, dorsal columns or peripheral neurons, since this is the case in most degenerative spinocerebellar ataxias.

3. Results: Prospective Cohort Studies on Long-Term Motor Training in Degenerative Cerebellar Ataxia

We retrieved $n = 578$ studies using the combinations of terms and MESH terms mentioned above. $N = 574$ studies were excluded as they did not meet at least one of the five inclusion criteria. 3 studies were identified that investigated high-intensity motor training exercises in a sizeable cohort of patients with degenerative spinocerebellar ataxia (for an overview, see Table 1). These studies examined the following training strategies: physiotherapy combined with occupational therapy; physiotherapy focusing specifically on exercises challenging complex coordinative behaviors (“coordinative physiotherapy”); and training with whole-body controlled videogames (“exergames”). One additional study was identified that presented only a case report (on exergame-based training in advanced multisystemic degenerative ataxia), yet it did also meet the inclusion criteria.

TABLE 1: Overview of high-intensity training studies in degenerative ataxia.

Physiotherapy combined with occupational therapy [36]			Coordinative Physiotherapy [34, 35]	Exergames training [43]
Number of patients	42		16	10
Type of disease	SCA6 (20), ADCA (6), and IDCA (16)		SCA6 (2), SCA2 (1), ADCA (1), IDCA (6), FRDA (3), SANDO (2), and SN (1)	FRDA (4), arCA (3), AOA2 (1), and ADCA (2)
Age ± SD (range)	62.5 ± 8.0 (range: 40–82)		61.4 ± 11.2 (range: 44–79)	15.4 ± 3.5 (range: 11–20)
Gender	22 males, 20 females		8 males, 8 females	5 males, 5 females
Duration of disease	9.8 ± 6.2 (7 months–30 years)		12.9 ± 7.8 (3–25 years)	
Baseline SARA	11.3 ± 3.8 (5–21.5)		15.8 ± 4.3 (11–24)	10.9 ± 2.3 (7–13.5)
Control	Crossover for short-term effect		Intraindividual controls for short-term effect	Intraindividual controls
Evidence class	Class Ib		Class III evidence	Class III evidence
Intervention	2 hours × 5 days + 1 hour × 2 days per week for 4 weeks		1 hour, 3 days per week for 4 weeks	1 hr × 4 per week for 2 weeks at lab; variable frequency at subjects' own motivation for 6 weeks at home
After training	No		Home-training protocols	No
Outcome measures	SARA, FIM, gait speed, cadence, FAC, and falls		SARA, gait speed, balance, BBS, GAS, and movement analysis	SARA, balance, ABC scale, DGI scale, GAS, and movement analysis
Assessment point	Baseline, post 0, 4, 12, and 24 weeks		4 weeks pre, baseline, and post 0, 8 weeks	2 weeks pre, baseline, and post 0
Main results	SARA and gait improved 12 wks but not 24 wks		SARA and gait improved 8 wks after rehabilitation only in patients with cerebellar ataxia not afferent ataxia	SARA and gait improved directly post rehabilitation; improvement correlated with individual's training intensity at home

SCA: spinocerebellar ataxia; FRDA: Friedreich's ataxia; IDCA: idiopathic cerebellar ataxia; ADCA: autosomal dominant cerebellar ataxia of unknown type; SANDO: sensory ataxic neuropathy with dysarthria and ophthalmoparesis caused by mutations in the polymerase gamma gene; SN: sensory neuropathy with cerebellar degeneration; arCA: autosomal recessive cerebellar ataxia of unknown type; AOA2: ataxia with oculomotor apraxia type 2; SARA: scale for the assessment and rating of ataxia; ABC: activity-specific balance confidence scale; BBS: Berg balance score; GAS: goal attainment scaling [42]; DGI: dynamic Gait index; FIM: functional independence measure [38]; and FAC: functional ambulation categories. Evidence was graded according to the Oxford Center for Evidence Based Medicine (CEBM) classification. This table presents details of the first three clinical studies of motor rehabilitation in larger cohorts in degenerative spinocerebellar disease [34–36, 43].

3.1. Physiotherapy Training

3.1.1. Physiotherapy Combined with Occupational Therapy. Physiotherapy generally targets one or several of the following domains, often combining a mixture of them: balance, gait, coordination, strength, endurance, and posture [37]. One recent study combined a mixed multidomain physiotherapy strategy with occupational therapy, testing this intervention in 42 patients with cerebellar degeneration by a randomized controlled study design with delayed-entry of the control group [36]. Subjects were trained for an aggregated amount of 12 hours per week for 4 weeks. The authors observed improvements of ataxia severity, gait speed, fall frequency, and activities of daily living as determined by the Functional Independence Measure (FIM) [38]. More specific clinical ataxia assessment by the scale for the assessment and rating of ataxia (SARA) revealed an improvement of 2.1 points directly after the 4-week intervention (immediate and delayed-entry group aggregated). The SARA scale extends from 0 to 40 points, with higher scores indicating more severe ataxia [39]. The natural disease progression of degenerative cerebellar ataxias is 0.4–2.2 points per year on the SARA scale depending on genotypes [25]. This implies that the average improvement achieved by this kind of training is equivalent to gaining back functional performance of one or more years of disease progression. Improvements were more prominent in trunk ataxia than in limb ataxia, and patients with mild ataxia severity experienced a more sustained improvement in ataxic symptoms and gait speed [36]. Long-term follow-up data were collected up to 24 weeks after the intervention. Although functional status tended to decline to baseline level within this period, more than half of the patients retained an improvement in at least 1 item of the outcome measures at 24 weeks compared to baseline. Patients with sustained improvement had less severe ataxia (i.e., lower SARA score) than those without sustained improvement, indicating a possible predictive value of the SARA score—and thus ataxia severity—at baseline. Due to the study design, training intensity did not differ between subjects, thus making correlations between training intensity and training benefits impossible. No quantitative movement analysis was performed and the assessments in this study were not blinded.

3.1.2. Coordinative Physiotherapy. One recent training study targeted specifically static and dynamic balance by a physiotherapy programme that focused on demanding coordinative exercises (“coordinative physiotherapy”) (for details on the exercises, see the following Table 4).

This strategy was tested in an intraindividual case-control design in 16 patients suffering from progressive ataxia due to cerebellar degeneration ($n = 10$) or degeneration of afferent pathways ($n = 6$) [34, 35]. Subjects were trained 1 hour per day, 3 days a week for 4 weeks under supervision of an ataxia expert physiotherapist at an ataxia centre, followed by 12-month home-training under the patient’s own guidance.

The 4-week centre-based physiotherapy led to an improvement of 5.2 points on the SARA score directly after the intervention. This implies an average achievement equivalent to gaining back functional performance of at

least two or more years of natural disease progression. Clinical assessments were additionally complemented by rater-independent quantitative movement analysis. This analysis revealed improvements in several aspects of gait like velocity or lateral sway as well as in the temporal and spatial variability of gait (e.g., step length, step cycle time). Variability in these measures has been discussed as a risk factor of falls in the elderly [40] as well as in subjects with cerebellar ataxia [41]. Moreover, it reduced temporal variability of intralimb coordination pattern in gait—a measure which has been shown to be specific for patients with cerebellar dysfunctions [8]. Patients with cerebellar ataxia profited more substantially from the intervention than patients with afferent ataxia. This discrepancy is most likely caused by a loss of afferent information in these patients, which removes necessary sensory inputs for adequate cerebellar processing.

Long-term effects and their translation to real-world functioning were assessed 12 months after the 4-week intervention period [35]. During these 12 months, subjects were trained by an individualized homework protocol combining different coordination exercises and degrees of difficulty, depending on the individual’s level of functioning and learning success. Despite the underlying progression of the disease, SARA scores were still significantly better at this long-term followup than at baseline for the cerebellar group by 3.1 points (Figure 1). This indicates a retention of training effects that is equivalent to gaining back at least one or more years of natural disease progression. The group of afferent ataxia patients was stable compared to baseline. Independent from the type of ataxia, training intensity in coordination exercises correlated significantly with differences in SARA scores after 1 year, indicating that retention of training effects depends crucially on continuous training [35].

The goal attainment score (GAS) [42] was used to capture translation of training-induced effects into real-world functioning. For this score, each patient selects a personally meaningful goal reflecting an individually important activity of daily life (e.g., see Tables 2 and 3). These goals were determined before training and achievements were rated along the following Likert scale: “–2” = functioning like at baseline, “–1” = less than expected outcome, 0 = expected outcome, +1 = greater than expected outcome, and +2 much greater than expected outcome. For all patients, the average rating was 0.57, that is, above the expected level of achievement.

3.2. Exergame-Based Training

3.2.1. Exergames Training in Mild-to-Moderate Degenerative Ataxia. Physiotherapy exercises might be complemented by (or used interchangeably with) whole-body training based on recently developed commercially available videogame technology (“exergames”). An exergame-based training strategy might have several advantages, in particular if used as a continuous long-term training for chronic diseases. (i) Exergame exercises involve highly motivational reward incentives and resort to diverse and stimulating exercise environments. (ii) Exergame-based training encompasses

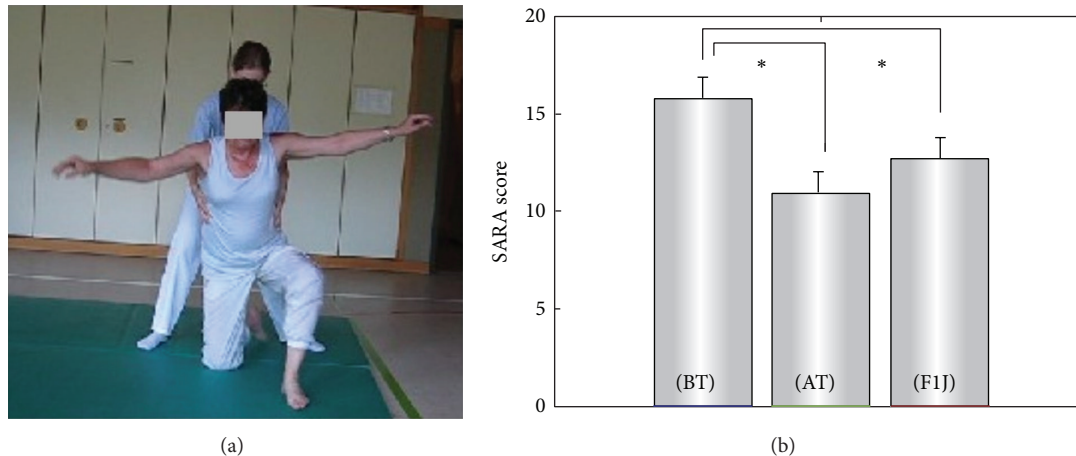


FIGURE 1: Coordinative physiotherapy. (a) Exemplary exercise of the training protocol: training of dynamic balance and multijoint coordination. (b) Group data of the clinical ataxia score SARA before training intervention (BT), after the four weeks training intervention (AT) and for follow-up assessment (F1J) after one year. Stars indicate significant differences between examinations (* $P < 0.05$). SARA: scale for the assessment and rating of ataxia ([35] reproduced with permission from Wiley).

TABLE 2: Personally selected goal of the goal attainment score for an exemplary individual with degenerative cerebellar ataxia (subject C4).

Individual goal: walking around a table with small distance without swaying	Score
The patient walks around the table mainly by touching the table	-2
The patient can walk around the table without touching the table most of the time	-1
The patient can walk around the table without touching the table	0
The patient can walk around the table without touching the table and he is able to look around sometimes	+1
The patient can walk around the table without touching the table and he is able to look around the whole time	+2

Five levels of goal attainment were defined before the intervention started. Scores range from -2 to 2 (-2~baseline, -1~less than expected outcome, 0~expected outcome, 1~greater than expected outcome, and 2~much greater than expected outcome [35]).

TABLE 3: Personally selected goals of the goal attainment scale and the scores obtained after the intervention period.

Patient	Goal	Score
C1	Walking on a narrow path (<50 cm)	2
C2	Walking up a staircase without using railway	2
C3	Reaching the mailbox in a distance of 600 without using a walking aid	0
C4	Walking around a table with small distance without swaying	1
C5	Walking without a walking aid over a distance >10 m	1
C6	Walking over a distance of about 300 m without a walking aid or a helping person	2
C7	Walking over a distance of 50 m with a trolley, without bumping with the feet into it	1
C8	Walking free on a small staircase (3 steps) in an alternating way with a distance of 1 m to the railway	-1
C9	Walking with a trolley over a distance of 50 m	0
C10	Walking without a walking aid over a distance of about 100 m	0
A1	Walking independently over longer distances (>500 m)	1
A2	Reducing danger of falling	0
A3	Walking a distance of 30 m with a full cup without spilling something	-1
A4	Walking with a trolley over a distance of 2000 m without dropping feet and strong support from the arms.	-1
A5	Walking over a distance of 100 m with a trolley and without bumping with the feet into it	2
A6	Walking with a trolley over a distance of 500 m	-1

Described goals correspond to score 0. Scores range from -2 to 2 (-2~baseline, -1~less than expected outcome, 0~expected outcome, 1~greater than expected outcome, and 2~much greater than expected outcome [35]).

TABLE 4: Exercises of the coordinative physiotherapy program.

Static Balance
(i) Standing on one leg.
(ii) Quadruped standing: stabilize the trunk and lift one arm.
(iii) Quadruped standing: stabilize the trunk and lift one leg.
(iv) Quadruped standing: lift one arm and the leg of the other side.
Dynamic Balance
(i) Kneeling: put one foot in front and back alternately.
(ii) Kneeling: put one foot to the side and back alternately.
(iii) Kneeling: put one foot in front, stand up, and put one leg back with kneeling alternately.
(iv) Standing: swing arms, see saw knees.
(v) Standing: step to the side.
(vi) Standing: step in front.
(vii) Standing: step back.
(viii) Standing: cross over step.
(ix) Climbing stairs.
(x) Walking over uneven ground.
Whole Body Movements to Train the Trunk-Limb Coordination
(i) Quadruped standing: lift one arm and the leg of the other side, flex arm, leg, and trunk, and extend arm, leg, and trunk alternately.
(ii) "Morning prayer" (Moshe Feldenkrais): kneeling: bend legs, arms, and trunk ("package sitting"); extend legs, arms, and trunk alternately.
(iii) Kneeling: sit beside the heel on the right side; kneeling: sit beside the heel on the left side alternately.
Steps to Prevent Falling and Falling Strategies In Order To Prevent Trauma
(i) Standing: step to the side, step in front, step back, and cross over step in a dynamic alteration.
(ii) Standing: the therapist pushes the patient in altered directions; the patient has to react quickly with fall preventing steps.
(iii) Standing: bend the trunk and the knees to touch the floor and erect the body alternately.
(iv) Standing: bend the trunk and the knees, touch the floor, and go down to quadruped standing,
(v) Standing: the therapist pushes the patient; the patient has to react quickly-bend and go to the floor in a controlled manner
(vi) Walking—the therapist pushes the patient—the patient has to react quickly, bend, and go to the floor in a controlled manner.
Movements to Treat or Prevent Contracture Especially Movements of Shoulders and Spine
(i) Extension of the spine: prone lying: push up the shoulder girdle from prone lying; prone lying on a wedge.
(ii) Rotation of the spine: supine lying: knees are bended, rotate the knees to the right and left side,
(iii) Flexion of the shoulder: supine lying: lift the arms in the direction of the head.

interactive exercises within rapidly changing environments, which could simulate and train patients' real-world activities and anticipatory coordination capacities. (iii) Patients with mobility impairments do not need to arrange access and transfer to external physiotherapy practices but can train within their own home environments.

Thus, taken together, exergames might present a novel, advantageous treatment tool for training patients with neurodegenerative diseases. It might allow patients to train coordinative exercises in a highly motivational and playful way at their own homes and with low financial costs. A directed exergames-based training program was recently investigated in 10 children with progressive spinocerebellar ataxia of a mild to moderate degree (i.e., all subjects were still able to walk without support) [43]. The investigators selected three commercially available Microsoft Xbox Kinect videogames, which were specifically chosen to target motor capacities known to be dysfunctional in ataxia, namely, goal-directed limb movements, dynamic balance, and whole-body coordination (Figure 2). The training program started with a 2-week laboratory training phase individually supervised and

directed by a physiotherapist, who introduced the games and adequate movement strategies to the subjects. During these two weeks, subjects were trained 1 hour per day, 4 days a week. This initial training phase was followed by 6 weeks of home-training phase during which the patients were asked to continue the exergame-based exercises at home. Effects of the training were assessed in an intraindividual control design. SARA ratings were performed in a blinded fashion, which was achieved by presenting videos of single SARA examinations of individual subjects in a random fashion to a rater who was blinded to the number of the specific examination. These rater-blinded assessments revealed a reduction by 2 SARA points on average after 8 weeks of training (Figure 2), indicating an achievement that is equivalent to gaining back at least one or more years of natural disease progression. The improvements in ataxia during the home-training were thereby dependent on the intensity of home-training: the more intensive the training periods at home, the higher the reduction in SARA gait and posture. The clinical improvement in ataxia severity was paralleled by improvements in quantitative measures of gait (lateral sway, step length

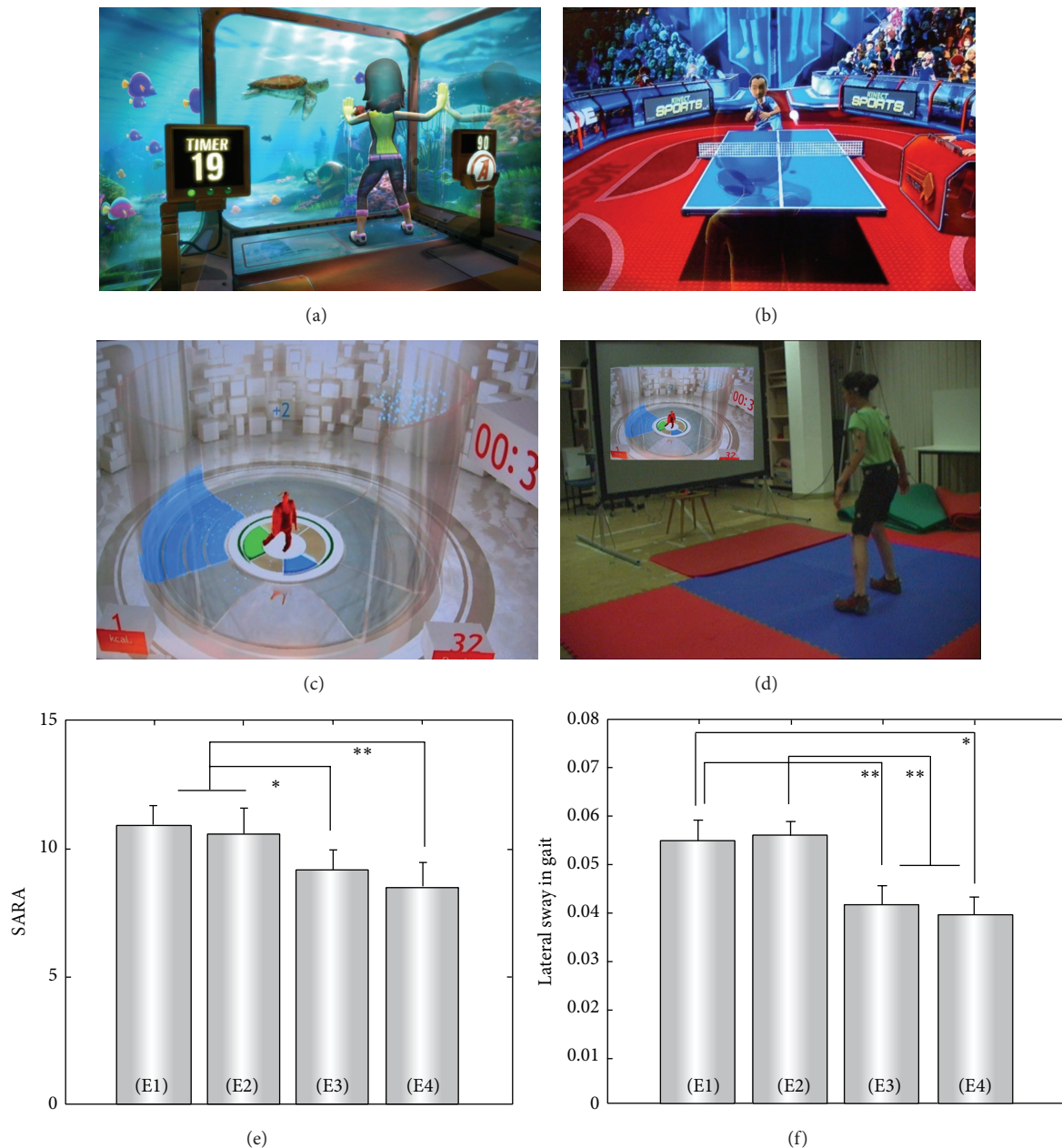


FIGURE 2: Exergame-based training. (a–c) Screenshots from the three XBOX Kinect games used in the training protocol. (a) 20000 leaks practice whole-body coordination and interaction with a dynamic environment; (b) table tennis practices goal-directed upper limb movements and dynamic balance, as well as movement timing; (c) light race practices goal-directed lower limb movements, fast movements, and dynamic balance. (d) Snapshot from the “Light Race” game. Patient CI performs dynamic stepping movements in order to control the avatar to step onto the highlighted areas on the floor (figures reproduced with permission from Microsoft Xbox Kinect (a), (b) and Ubisoft (c), (d)). (e, f) Group comparisons of the clinical ataxia scores (SARA) and lateral sway in gait at examinations E1–E4. Patients were examined four times: two weeks before intervention (E1), immediately before the first training session (E2), after the two-week lab-training period (E3), and after the six-week home-training phase (E4) [43]. Stars denote significance: * $P < 0.05$, ** $P < 0.01$.

variability) [43] (Figure 2) and, even more importantly, by improvements in ataxia-specific dysfunctions like multijoint coordination and dynamic stability [44]. This included complex whole-body movements highly relevant for everyday living, for example, rapid stepping movements to compensate for gait perturbations and to prevent falls. Improvements

transferred also to other movements, indicating a generalization effect of the underlying control mechanisms induced by exergames training [44]. These findings demonstrate that exergames training yields a specific effect on ataxia and dynamic balance which goes beyond a mere improvement in subjects' game scores, motivation, and fitness. Training was

highly motivational for all participating subjects throughout the whole training period [43].

In sum, this study suggests that directed training of whole-body controlled videogames might present a highly motivational, cost-efficient, and home-based rehabilitation strategy to train dynamic balance and interaction with dynamic environments for subjects with chronic coordination disturbances.

3.2.2. Exergames Training in Advanced and Multisystemic Ataxia. Exergame-based training might improve coordination in subjects with mild-to-moderate spinocerebellar ataxia. Yet, it is still an open question whether it is also effective in subjects with advanced degenerative cerebellar disease who are already wheelchair-bounded and, moreover, where ataxia is part of a multisystemic disease affecting many additional pathways of the central and peripheral nervous system. These subjects are largely considered to benefit only poorly from treatments which is indicated, for example, by the fact that they are commonly excluded from current drug treatment trials [45, 46], thus leaving them without prospects of access to novel treatments.

A recent case study provided first proof-of-principle evidence that exergame-based coordinative training might indeed serve as an effective treatment even for advanced, multisystemic degenerative ataxia [47]. The investigators used a sequentially structured 12-week coordinative training program based on specifically selected, commercially available Nintendo Wii games in a child with advanced ataxia telangiectasia (AT) who was already largely wheelchair-bounded. Outcomes were assessed in a rater-blinded intraindividual control design. The authors observed an improvement of 4.4 points on the SARA scale, which was most pronounced in posture and residual gait function. Correspondingly, subjective achievement ratings in the GAS show marked balance improvements in sitting and stance [47]. These results seem to indicate that, despite advanced multisystemic disease (including oculomotor and cognitive deficits), exergame-based coordinative training might lead to substantial effects which translate into daily living. However, these preliminary results need to be confirmed in a larger cohort study before firm conclusions can be drawn.

4. Discussion

The above described studies provide first evidence for sizeable cohorts that high-intensity motor training might be effective in degenerative ataxia. More specifically, they provide proof-of-concept evidence that

- (1) patients with degenerative ataxia benefit from coordinative training which might be based either on physiotherapy or on exergames;
- (2) improvements are equal to regaining 1 or more years of natural disease progression;
- (3) improvements are not due to unspecific changes but due to recoveries in ataxia-specific dysfunctions;

- (4) retention of training effects depends on the continuity of training;
- (5) even subjects with advanced neurodegeneration benefit from these therapies;
- (6) even children with severe disease can be highly motivated to train throughout the whole demanding program and that they experience feelings of success about their own movements.

4.1. Open Questions and Future Studies. Albeit promising, the aforementioned studies have important limitations. These limitations stimulate new research questions that might guide the field in the next years. Larger cohort studies are warranted to confirm the aforementioned findings. As degenerative ataxias belong to “orphan diseases” with a prevalence of approximately 6:100.000 [48], it will require coordinated multicenter efforts to aggregate larger cohorts. These cohorts should be more homogeneous. The phenotypic and genetic variability between different degenerative ataxias is large, including different disease progressions and different comorbid affection of additional neural systems [21, 49, 50]. Thus, future studies should ideally resort to cohorts with prespecified, homogenous genotypes. Moreover, they should aim at using a randomized control design to yield higher levels of evidence. The intraindividual control design used by three of the four aforementioned studies [34, 43, 47] has several attractive advantages, since subjects are here taken as their own controls and thus between-group differences in disease progression and comorbid affection of different neural systems can be ruled out. However, a randomized control design is still methodologically superior, and a delayed-entry design as employed in the study of Miyai and colleagues [36] guarantees that also the control group will receive the benefits of motor training. Moreover, studies should use a multicenter design, as only this design could prove that the specific training is indeed transferable to other centers and therapists.

Future studies should also focus more specifically on identifying predictors for training success. The type of ataxia might serve as a predictor, as, for example, indicated by the finding of Ilg and colleagues that patients with afferent ataxia benefit less than patients with cerebellar ataxia [34, 35]. However, this might not generally be true as younger patients with afferent ataxia (namely, Friedreich’s ataxia) still benefitted well from XBOX-based exergame training [43]. Another predictor might be severity of ataxia at baseline, as suggested by the finding of Miyai and colleagues that patients with more severe ataxia had less sustained improvement by training [36]. But, again, this might not generally be true, as indicated by the finding of Synofzik and colleagues that a wheelchair-bound subject with advanced degenerative ataxia still achieved a remarkable improvement of 4.4 points on the SARA scale [47]. Finally, the specific level of residual cerebellar integrity might be a predictor of the capacity to improve motor performance. Studies from subjects with focal cerebellar lesions (e.g., due to stroke or tumor) have indicated that in particular the integrity of the deep cerebellar nuclei might determine future rehabilitation success [51, 52].

The changes in neural mechanisms and substrates underlying the training effect in degenerative ataxias are still largely unclear. Is the degenerating cerebellum still able to adapt motor coordination or, instead, is the learning deficit compensated by other brain structures? In an attempt to depict the brain changes that contribute to improvement of motor function, Burciu et al. [53] performed a voxel-based morphometry (VBM) study in patients with cerebellar degeneration. A two-week postural training resulted in a significant improvement of balance in degenerative patients. Comparing gray matter volumes before and after training revealed an increase primarily within nonaffected neocortical regions of the cerebellar-cortical loop, more specifically the premotor cortex. Gray matter changes were observed within the cerebellum as well but were less pronounced. Thus, these first data suggest that training may lead to activation and plasticity of compensatory networks and, to a smaller extent, even of remaining cerebellar circuitry itself. Further imaging studies on neurorehabilitation strategies will lead to a better understanding of the underlying pathomechanisms of disordered motor performance and learning. This might help to tailor physiotherapy to the specific needs of patients with cerebellar ataxia.

4.2. Preliminary Implications for Practice: Physiotherapy versus Exergames—A Wrong Dichotomy. Despite their limitations, the aforementioned studies provide some preliminary hints on the relation between physiotherapy versus exergame training in long-term training protocols. These hints stimulate future investigations, validating these ideas and exploring them in more detail.

The experience from these studies indicates that exergame-based training can and should not replace physiotherapy. It might rather serve to complement physiotherapy-based programs by helping subjects to achieve and maintain the required training intensity even over a long training period and by practicing specific coordination skills such as rapid adaptation to dynamically changing environments and updating of predictions to novel external events. These skills are highly needed in real-world situations where subjects have to adequately react under time pressure to constantly changing environmental conditions and to accurately anticipate novel events and their impact for one's own sensorimotor system. It was shown that both of these skills are impaired in degenerative cerebellar disease [54, 55], yet they are less trained by conventional physiotherapy compared to exergames. Due to the training in an interactive, constantly changing environment with many novel unexpected events, exergames better simulate real-world situations. Well-selected games (Figure 2) allow to efficiently improve these highly valuable coordination skills, as shown recently [43, 47, 56].

However, the experience from the abovementioned studies also reveals that any exergame-based training needs to be initiated and supervised to a variable degree by a physiotherapist. The specific expertise of this professional is needed to select appropriate exergames according to each individual's coordinative capacities, degree of impairment, and current

treatment goals. Only this selection and supervision can ensure that the patient is neither over- or underchallenged which would quickly lead to a lack of motivation. Moreover, it ensures that the patient is not predisposed to risky movements which might lead to falls and other harms. Finally, it seems preferable that, at least during the first training sessions, the physiotherapist would actively coach the patient how to make adequate complex coordination movements when trying to solve the exergame challenges. We have observed that ataxia patients initially often try to play these games by reducing their movement repertoire even more, trying to keep their center of mass within their base of support by making themselves "stiff" and by actually avoiding complex movements [43, 44]. If entrenched by continued playing, this derivative compensatory movement strategy might lead to a further loss of coordination skills, that is, trigger a downward spiral, thus indicating that exergame-based training might even be *harmful* if not applied adequately. A parallel training and supervision by a physiotherapist likely help the patient to avoid such wrong movement strategies and to relearn to make complex movement sequences, even if they seem risky in the beginning.

4.3. Recommendations for Clinical Practice. Based on the aforementioned studies, a new concept for ataxia training in clinical practice emerges. This concept still has to be validated in practice and should thus be seen as a preliminary rather than a definitive suggestion. Yet it might stimulate future research and clinical rehabilitation practice.

This concept is characterized by the idea that rehabilitation in degenerative ataxias should optimally resort to a large array of different training strategies which should be individually tailored according to each individual's ataxia type, disease stage, and personal training preferences. In very *early stages of ataxia*, even demanding sportive exercises might be selected which place high challenges to the coordination system, for example, table tennis, squash, or badminton. These real-world sports might be complemented by demanding XBOX Kinect games (e.g., "Light Race" or "20.000 Leaks") or Wii games (e.g., "PhysioFun"). These games might be played on an elastic mattress to increase the coordinative challenge even more. In *mild-to-moderate ataxia stages*, a coordinative physiotherapy program under the guidance and supervision of a professional physiotherapist receives major importance [34]. This might include the training of secure fall strategies in addition of training to avoid falls. The exergame-based training component might switch to a little less challenging XBOX or Wii games, for example, "tightrope walk" or "ski slalom." In *advanced ataxia stages*, no clear evidence-based physiotherapy training program does yet exist. However, in severe cases, in which free standing and walking is not possible anymore, treadmill training [28–30] with potential weight support may be helpful to increase walking capabilities (with the use of mobility aids) and to preserve general fitness as far as possible [10]. The exergame-training component has to be limited to Wii games, as XBOX Kinect games cannot be played by subjects who are bound to a sitting position. Here, subjects will be seated

onto the Wii balance platform which then serves to detect shifts of weight of the trunk. Candidates for appropriate Wii games include “penguin slide,” “table tilt,” or “bubble balance” [47]. Taken together, such individualized tailored training strategies might help to maximize the function of each individual subject in his or her particular disease state, and might—at least in some cases—slow down a possible downward-spiral of ataxia-related immobility and further deterioration of coordinative functions.

In conclusion, rehabilitation for degenerative cerebellar disease will remain a challenge for patients, physicians, and therapists. However, recent advantages in both clinical rehabilitation and research on motor adaptation in cerebellar disease will stimulate further studies and hopefully lead to broader knowledge in this challenging field of motor rehabilitation and finally to an improvement of the patients’ quality of life.

Abbreviations

GAS: goal attainment score

SARA: scale for the assessment and rating of ataxia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Dr. Matthis Synofzik contributed to the design and conceptualization of the study, acquisition of clinical data and analysis and interpretation of data, and drafting of the paper. Dr. Winfried Ilg contributed to the design and conceptualization of the study, acquisition of clinical data and analysis and interpretation of data, and drafting of the paper.

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Clinical Study

The Effects of High-Intensity versus Low-Intensity Resistance Training on Leg Extensor Power and Recovery of Knee Function after ACL-Reconstruction

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Objective. Persistent weakness is a common problem after anterior cruciate ligament- (ACL-) reconstruction. This study investigated the effects of high-intensity (HRT) versus low-intensity (LRT) resistance training on leg extensor power and recovery of knee function after ACL-reconstruction. **Methods.** 31 males and 19 females were randomized to HRT ($n = 24$) or LRT ($n = 26$) from week 8–20 after ACL-reconstruction. Leg extensor power, joint laxity, and self-reported knee function were measured before and 7, 14, and 20 weeks after surgery. Hop tests were assessed before and after 20 weeks. **Results.** Power in the injured leg was 90% (95% CI 86–94%) of the noninjured leg, decreasing to 64% (95% CI 60–69%) 7 weeks after surgery. During the resistance training phase there was a significant group by time interaction for power ($P = 0.020$). Power was regained more with HRT compared to LRT at week 14 (84% versus 73% of noninjured leg, resp.; $P = 0.027$) and at week 20 (98% versus 83% of noninjured leg, resp.; $P = 0.006$) without adverse effects on joint laxity. No other between-group differences were found. **Conclusion.** High-intensity resistance training during rehabilitation after ACL-reconstruction can improve muscle power without adverse effects on joint laxity.

1. Introduction

Anterior cruciate ligament (ACL) injuries of the knee are amongst the most common major injuries in sport [1]. People with a high preinjury level of sports participation are often recommended to undergo an ACL-reconstruction [2] and these people are also likely to choose ACL-reconstruction [3]. The goal of a rehabilitation program after an ACL-reconstruction is to regain mobility and muscle function and ultimately to return to sports participation [4]. However,

despite postoperative rehabilitation, deficits in muscle function of the operated leg persist up to several years postsurgery [5–12]. These deficits in muscle function are of much concern to clinicians and researchers because a regained muscle function is important for dynamic joint stability [13, 14].

Several studies have demonstrated moderate-to-strong associations ($r = 0.34$ – 0.74) between thigh muscle strength (primarily quadriceps strength) and knee function (assessed as hop tests) after ACL-reconstruction [15–18]. In addition, it has been shown that inadequate quadriceps

strength contributed to altered gait patterns following ACL-reconstruction [19]. People who have regained high levels of quadriceps strength after ACL-reconstruction are more likely to return early to their previous sports activity and at the same level as before the injury [20]. Thus, it seems that quadriceps strength is an important determinant for satisfaction after the ACL-reconstruction [17]. In addition, it has been suggested that quadriceps weakness is a risk factor for developing osteoarthritis [21–23].

There is still no consensus regarding the optimal rehabilitation program after ACL-reconstruction [4, 24]. Current programmes emphasize full passive knee extension, immediate weight bearing as tolerated, and functional exercises [4, 25]. It has been suggested that these programs focus too much on functional low-intensity and sports-specific exercises and that weight training intensity may be too low to increase muscle strength to a satisfactory level [26, 27]. Most studies have measured muscle strength (force) after ACL-reconstruction; however, muscle power (force \times velocity) may provide a more sensitive and sports-specific measure of muscle function [5, 11, 28, 29]. The effectiveness of traditional resistance training methods for developing maximal power has been questioned because this type of training has been suggested to increase maximal strength at slow movement velocities rather than improving other components contributing to maximal power production [29].

The aim of the ACL-reconstruction surgery is to create a mechanically stable knee and the aim of the rehabilitation is to create a functionally stable knee. The effects of various rehabilitation exercises in both open and closed kinetic chain have been discussed extensively in the literature, but few prospective randomized studies following ACL-reconstruction have been conducted to investigate these issues [30]. The concern has mainly been about the risk of elongation of the ACL graft and mechanical instability of the knee resulting from early isolated quadriceps resistance training [31]. There is a consensus that open kinetic chain exercises with a focus on endurance do not increase graft laxity and have favourable effects on quadriceps strength, but there is still uncertainty about the optimal timing of introduction of these open kinetic chain exercises [24].

To our best knowledge, the effect of high-intensity and low-intensity resistance training on muscle function in individuals who have undergone ACL-reconstruction has not been investigated previously. Therefore, the objective of the present study was to investigate whether individuals, who perform high-intensity resistance training (HRT) as part of their rehabilitation after ACL-reconstruction, will achieve greater improvements in leg extensor muscle power and greater improvements in knee function compared with individuals performing low-intensity resistance training (LRT) without any negative effect on mechanical instability. We hypothesized that HRT would be superior to LRT for regaining muscle power and knee function, respectively.

1.1. Study Design. The study was designed as a single blinded, randomized, clinical trial of two types of resistance training as part of the rehabilitation program after ACL-reconstruction. All participants gave written informed consent before taking

part in the study. The study protocol was in compliance with the Helsinki Declaration and the study was approved by the local ethics committee (KF01-008/04).

2. Material and Methods

2.1. Participants. Men and women aged 18–45 years with isolated ACL rupture who underwent an elective primary ACL-reconstruction and subsequent rehabilitation at Bispebjerg Hospital were recruited consecutively via the operating room list. Subjects were excluded if they had (1) bilateral ACL injury, (2) a previous ACL-reconstruction, (3) repair of meniscus in the index knee within the last 5 months, or (4) earlier intra-articular fracture or osteoarthritis of the knee or (5) if the conventional rehabilitation program could not be followed (Figure 1).

2.2. Surgical Procedures. ACL-reconstructions with the bone-patellar tendon-bone or hamstrings tendon (four-leg semitendinosus-gracilis) grafts were carried out by experienced orthopaedic surgeons. The 20-week rehabilitation program was independent of graft choice. Studies comparing ACL-reconstruction using either of these two grafts have shown very similar clinical results [32–34]. However, there is evidence of a greater deficit in knee extensor muscle strength following ACL-reconstruction with patella tendon graft and a lower deficit in knee flexor muscle strength following ACL-reconstruction with hamstrings graft although not all studies have reported muscle strength differences between the two types of surgery [35, 36]. Immediately after the ACL-reconstruction, the participants were randomized to either HRT or LRT, which started at week 8. A similar distribution of sex, graft, and meniscus repair in the two groups was ensured by using the minimisation method with the aid of a computer program [37] for the randomization.

2.3. Rehabilitation Protocol. All participants underwent a standardised 20-week rehabilitation program, which started immediately after surgery. The initial focus was on improving postoperative pain and swelling, range of motion, and muscle strength. Full range of motion and weight bearing according to the person's tolerance was allowed and the participants performed isometric quadriceps contractions and dynamic exercises for the hamstring muscles. From week 4 the individuals participated in a supervised one-hour group-based program twice weekly with the main focus on neuromuscular-, functional-, and sports-specific training. Participants who underwent a meniscus repair in combination with the ACL-reconstruction had restricted range of motion during the first five weeks after surgery and were not allowed to start on the group-based program until week 7 but otherwise they received the same program.

A 30-minute progressive, weight training program was initiated 8 weeks after the ACL-reconstruction and was conducted subsequent to the group-based program. The resistance (training loads) was increased when the individual could do more repetitions than the number specified in the

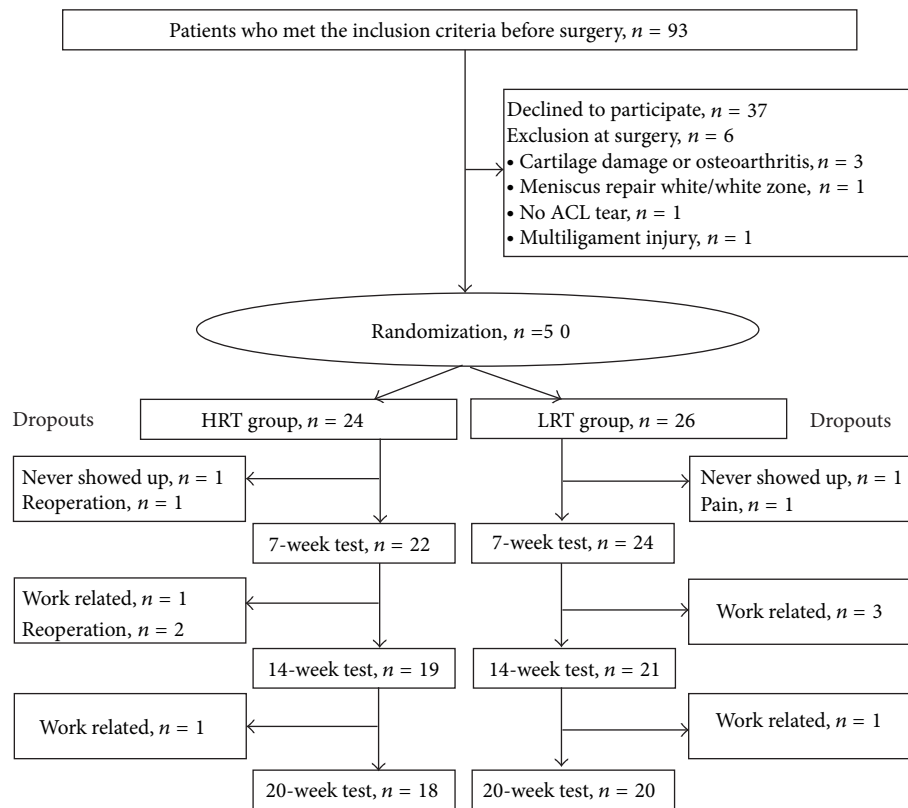


FIGURE 1: Trial profile. 50 patients were randomized and 6 from each group dropped out of the study. None of the dropouts were related to adverse effects of the strength training. Work related dropouts were because participants were unable to attend group training during office hours.

weight training protocol [29]. The exercises were performed at a slow speed to ensure full control of the movement. During weight training pain was allowed, but if the participants reported pain of more than 5 on a VAS, range of motion and/or load was reduced. The HRT-program included bilateral and unilateral exercises, that is, leg press (from 90 to 0 degrees in knee), knee flexion in the prone position (0–90 degrees), and seated knee extension (90–0 degrees). The first two weeks of the weight training program served as a familiarization period and thereafter loading increased by lifting weights to failure from 20 to 8 RM (Table 1) with a 2-minute rest period between the sets. However, because the participants had undergone ACL-reconstruction the increase in load happened slowly and high-intensity resistance training started at week 14. The LRT-program included leg press (from 90 to 0 degrees in knee), knee flexion in the prone position (0–90 degrees), and heel raises in the standing position (weight west) with loading increased by lifting loads to failure from 30 to 20 RM (Table 1) and a 1-minute rest period between the sets.

2.4. Data Recording. The participants were assessed by the same blinded investigator before and 7, 14, and 20 weeks after surgery. Three external physical therapists, blinded for group allocation, completed all the measurements in the same standardised way regarding test protocol and order of measurements. Before the assessments of muscle power and knee

function, the participants completed a 10-minute warmup on a stationary bike. The nonoperated healthy leg was always tested first. Any pain during the tests was measured on a VAS and registered. At the pretest, data regarding preinjury sports were collected.

2.4.1. Objective Outcome Measures. Knee joint laxity was evaluated with the KT-2000 arthrometer (MEDmetric Corporation, San Diego, CA) at 15 Lbs (67N) and 20 Lbs (89N) anterior-posterior directed loads [38]. The measurements continued until the value was reproduced. The value of the 20 Lbs test was used for statistical analyses. KT-2000 instrumented examination of knee laxity in the ACL injured leg has shown relatively high intratester reliability (ICC = 0.95) [38].

Measurements of maximal leg extensor muscle power (force × velocity) were performed using the Leg Extensor Power Rig (Queen's Medical Centre, Nottingham University, UK) according to procedures described elsewhere [39]. In brief, leg muscle power was measured during unilateral leg extension with the participants seated with a flexed knee and the foot positioned on the dynamometer pedal. The free foot rested on the floor. The participants were instructed to push the pedal forward as hard and fast as possible. The extension movement took 0.25–0.4 seconds and the final angular velocity of the flywheel was used to calculate the average leg extensor power produced in the push [39].

TABLE 1: The 12-week weight training protocol for the high- and low-intensity resistance training.

Week	HRT-group Sets \times repetitions (load)		LRT-group Sets \times repetitions (load)	
	Bilateral	Unilateral	Bilateral	Unilateral
8*	1 \times 20 (20RM)	2 \times 15 (20RM)	1 \times 30 (30RM)	1 \times 20 (30RM)
9*	1 \times 20 (20RM)	3 \times 15 (20RM)	1 \times 30 (30RM)	2 \times 20 (30RM)
10 + 11	1 \times 15 (15RM)	3 \times 12 (15RM)	1 \times 20 (20RM)	2 \times 20 (20RM)
12 + 13	1 \times 12 (12RM)	3 \times 10 (12RM)	1 \times 20 (20RM)	2 \times 20 (20RM)
14–20	1 \times 8 (8RM)	3 \times 8 (8RM)	1 \times 20 (20RM)	2 \times 20 (20RM)

HRT: high-intensity resistance training; LRT: low-intensity resistance training.

RM: repetition maximum. 1RM is the most weight you can lift for one repetition. 15RM is the most weight you can lift for 15 repetitions.

* Familiarization period.

Measurements were repeated until maximal power output could not be increased further. At least five repetitions were performed and the highest value was used for data analysis.

Knee function was assessed with a one-legged single hop and triple hop test for distance before and 20 weeks after surgery. The two tests were performed by hopping forward as far as possible and landing on the same leg with the hands on the back [40, 41]. Before each hop test, the participants performed two practice trials. The distance hopped was recorded (cm from toe to heel), and the best of three trials for each leg was used for data analysis.

2.4.2. Self-Reported Outcome Measures. Self-reported knee function and knee associated problems were evaluated by use of the knee injury and osteoarthritis outcome score (KOOS) and the Lysholm score and activity level by the Tegner activity scale before and 7, 14, and 20 weeks after surgery. All scores were used as patient-administered surveys.

KOOS is a self-explained patient-administered instrument to assess the patients' opinion about their knee and associated problems [42]. KOOS consists of 5 subscales: (1) pain, (2) other (knee) symptoms, (3) function in daily living (ADL), (4) function in sport and recreation (sport/rec), and (5) knee-related quality of life (QOL) with a score for each continuous subscale from 0 (extreme symptoms) to 100 (no symptoms).

The Lysholm score, which consists of 8 different items: limp, support, pain, instability, locking of the knee, swelling, stair-climbing, and squatting, and the Tegner activity scale were used to assess function and physical activity [43–46].

2.5. Statistical Analyses. Since leg extensor power assessed by the Power Rig device has never been used as a study outcome measure in people with ACL injury or -reconstruction, a prior sample size was calculated to $n = 20$ in each group based on knee extension muscle strength [20] and one-legged single hop for distance with a requirement of a MIREDF at 20%, power at 80%, and a 5% significance level and allowing for a drop out of 20% in both groups.

Results for objective outcome measures are presented as least square mean, standard error, 95% confidence intervals, and self-reported outcomes measures as median and interquartile range (25–75 percentile). We used $P < 0.05$ as

level of significance for testing of main effects and $P < 0.01$ for post hoc tests to account for multiple testing. Between-group differences at baseline were tested with an unpaired t -test for objective outcome measures, the Mann-Whitney test for self-reported outcomes measures, and the Chi squared test for numerical data. To determine differences in change over time between groups in the self-reported outcomes the Mann-Whitney test was used. Within-group changes over time were analyzed with Friedman's test or Wilcoxon signed rank test. We used two-way ANOVA (Proc Mixed of SAS version 9.3) to determine differences between groups from before to after surgery and changes during the resistance training phase, respectively. Power for the injured leg was normalized to the baseline value of the noninjured leg (normalized power). Group, time, and group by time were entered in the model as fixed factors. Subject was entered as a random factor. The ANOVA of changes during the resistance training phase was controlled for severity of postsurgery weakness, by including normalized muscle power at week 7 (i.e., first measurement after surgery before initiation of resistance training in both groups) as a covariate. We did not impute missing data as all methods of data imputation have limitations. The mixed procedure of SAS inherently accounts for missing values. Analysis of joint laxity was performed in a similar way, however, not expressed as a percentage of the noninjured leg but as the difference, as this is common for joint laxity.

3. Results

Fifty people were randomised (Figure 1) and there were no differences between participants in the HRT- and LRT-groups prior to the ACL-reconstruction except that the time between injury and surgery was longer in the HRT-group (Table 2). Prior to their ACL injury, 76% of the participants had participated in knee-demanding sports such as soccer, team handball, badminton, squash, fencing, martial arts, or basketball. Weekly time spent on sports activities was 4 hours or more for 58% of the participants.

Thirty-eight participants completed the 20-week rehabilitation program (Figure 1). The two graft options were equally represented among the dropouts, that is, 4 ACL-reconstructions with hamstring graft and 2 ACL-reconstructions with patella tendon graft in the HRT- and

TABLE 2: Baseline characteristics of the participants 1-2 weeks before ACL-reconstruction.

Variable	HRT-group	LRT-group	P value
Number (<i>n</i>)	24	26	
Age (year)	29.2 ± 1.5	29.2 ± 1.1	0.976
Sex: M/F (<i>n</i>)	15/9	16/10	0.994
Body weight (kg)	76.1 ± 2.7	77.2 ± 2.6	0.754
Graft: BPTB/STG	13/11	14/12	0.982
Months from injury to surgery	40.3 ± 10.0	16.8 ± 4.9	0.043
Meniscus tear (<i>n</i>)	11	13	0.877
Repair with arrows	5	6	
Resection, current/previous	6	7	
Cartilage damage (<i>n</i>)	7	10	0.448
Leg extensor muscle power			
Ratio ACL/healthy limb %	90.5 ± 2.8	89.4 ± 3.9	0.814
Knee joint laxity			
Diff. ACL and healthy limb (mm)	2.1 ± 0.3	2.8 ± 0.4	0.184
One-legged single hop			
Ratio ACL/healthy limb %	79.7 ± 4.7	68.8 ± 3.7	0.077
One-legged triple hop			
Ratio ACL/healthy limb %	86.4 ± 3.5	82.1 ± 3.2	0.367
Tegner activity scale (0–10)	3 (2–5)	2 (2–4)	0.292
Lysholm score (0–100)	70 (52–83)	66 (56–81)	0.771
KOOS (0–100)			
Pain	85 (67–94)	79 (67–90)	0.514
Symptoms	89 (70–96)	80 (62–90)	0.131
ADL	93 (75–97)	89 (79–97)	0.936
Sport	70 (49–76)	60 (40–81)	0.499
QOL	44 (38–56)	44 (36–50)	0.467

Data are reported as mean ± SE except self-reported surveys, which are presented as median (interquartile range).

HRT: high-intensity resistance training; LRT: low-intensity resistance training; BPTB: bone-patellar tendon-bone graft; STG: four-legged semitendinosus-gracilis graft; KOOS: knee injury and osteoarthritis outcome score with subscales (0: extreme symptoms, 100: no symptoms); pain, other symptoms, ADL: function in daily living, sport/rec: function in sport and recreation, and QOL: knee-related quality of life.

LRT-groups, respectively. There were no between-group differences in cartilage and meniscus damage but the participants who dropped out had greater preoperative knee laxity in the ACL injured knee (data not shown). This was due to two participants who had very high knee laxity before surgery. At 7 weeks after surgery their knee laxity was similar (i.e., within the same range) to that of the other participants. When the strength training started there was no difference between those who dropped out later ($n = 10$) and those who completed the study (HRT, $n = 18$; LRT, $n = 20$). Otherwise, they did not differ statistically from those who completed the rehabilitation program. Compliance in the two groups was similar; that is, participants in the HRT-group completed on average 22 (19–24) and participants in the LRT-group completed 20 (19–22) out of 24 training sessions.

3.1. Maximal Muscle Power. Before surgery power in the injured leg was 90.1% (CI: 86–96%) of the noninjured leg in both groups. At the first measurements after surgery (i.e., at week 7) this value had decreased to 64.3% (CI: 60–69%) in both groups. Figure 2 and Table 3 show changes in muscle power from week 7 to 20, that is, during the 12-week

resistance training period. During this period we found a significant *group by time* interaction for leg extensor power ($P = 0.020$). Power was regained to a greater extent in HRT-group than LRT-group at weeks 14 and 20, Figure 2 and Table 3.

3.2. Knee Joint Laxity. Knee joint laxity was significantly reduced from before to 7 weeks after surgery in both groups and did not change in either of the groups from 7 to 20 weeks. No between-group differences for change in side-to-side difference were found at any time points (Table 3).

3.3. Knee Function. The changes in knee function over time did not differ between the groups for one-legged single hop ($P = 0.566$) and triple hop tests ($P = 0.880$). Further, none of the groups had regained their knee function after the intervention period. At twenty weeks after surgery, the ratio was 69.1% ± 5.2 (CI = 58.4; 79.8) and 75.3% ± 4.0 (CI = 67.2; 83.4) for one-legged and triple hop, respectively, in the HRT-group. The ratios were 65.1% ± 5.1 (CI = 54.8; 75.4) and 68.1% ± 3.8 (CI = 60.3; 76.0) for one-legged and triple hop, respectively, in the LRT-group.

TABLE 3: Change in muscle power and knee joint laxity during the intervention period.

	7 weeks after surgery		14 weeks after surgery		20 weeks after surgery	
	HRT	LRT	HRT	LRT	HRT	LRT
Leg extensor power	64.0 ± 3.4 (57.1; 70.8)	64.8 ± 3.2 (58.3; 71.3)	84.1 ± 3.4* (77.3; 91.0)	73.3 ± 3.3 (66.6; 79.9)	97.5 ± 3.6** (90.3; 104.7)	83.5 ± 3.2 (77.0; 90.0)
Knee joint laxity	1.2 ± 0.3 (0.7; 1.7)	1.3 ± 0.2 (0.8; 1.8)	1.3 ± 0.3 (0.8; 1.8)	0.9 ± 0.3 (0.4; 1.4)	1.4 ± 0.3 (0.9; 2.0)	1.1 ± 0.3 (0.6; 1.6)

Power results are presented as least square mean ratios (ACL limb normalized to the presurgery value for the healthy limb multiplied by 100) ± SE (CI). Knee joint laxity results are presented as least square mean side-difference in mm ± SE (CI).

HRT: high-intensity resistance training; LRT: low-intensity resistance training. Significant between-group differences in regain of muscle power: * $P = 0.027$, ** $P = 0.006$.

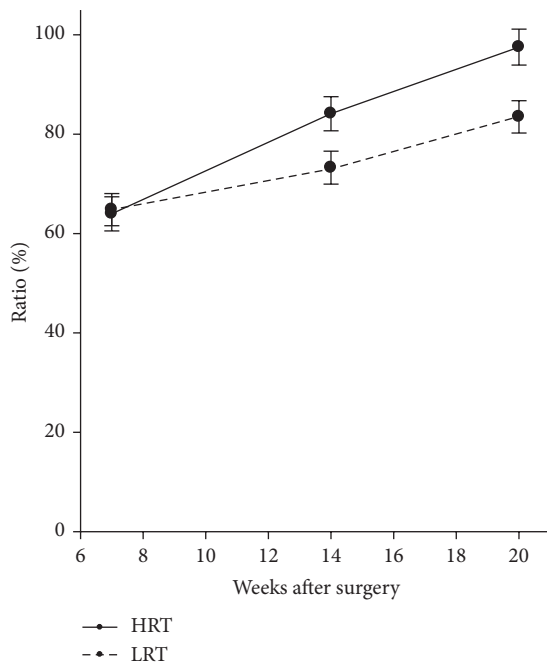


FIGURE 2: Changes in leg extensor muscle power from pre- to postsurgery. Results in muscle power are presented as least square mean ratios, that is, ACL limb normalized to the presurgery value for the healthy limb multiplied by 100 and SE. There were significant between-group differences at 14 weeks ($P = 0.027$) and at 20 weeks ($P = 0.006$) after surgery.

3.4. Self-Reported Knee Function. During the rehabilitation significant changes occurred for all the subscales in the KOOS ($P = 0.0001$ – 0.030) and Lysholm score ($P < 0.0001$) but there were no significant differences between the two groups at any time points (Table 4). During the first 7 weeks postoperatively KOOS subscale symptoms decreased significantly ($P < 0.01$) in the LRT-group and function in sport and recreation in the HRT-group. All KOOS subscales except knee-related quality of life increased significantly ($P < 0.01$) in both groups from 7–20 weeks after surgery. The values 20 weeks postoperatively were not significantly different from the presurgery values ($P = 0.173$ – 0.909), except for the knee-related quality of life, which was higher in the LRT-group ($P = 0.009$). The Lysholm score was unchanged from before surgery to 7 weeks after surgery in both groups,

but subsequently increased significantly ($P < 0.0001$) and remained elevated 20 weeks after surgery compared to before surgery ($P < 0.01$) (Table 4).

4. Discussion

The present study showed that leg extensor muscle power improved to a greater extent in the HRT-group compared with the LRT-group during the weight training period from 8 to 20 weeks after surgery. Thus, the initial hypothesis that HRT is superior to LRT for regaining muscle power was confirmed by the presented data.

Furthermore, the study demonstrated a substantial decline in leg extensor muscle power in the ACL operated limb 7 weeks after surgery (Figure 2) despite the fact that the rehabilitation program started immediately after surgery. To the best of our knowledge, only one study by Morrissey et al. [47] has documented changes in muscle function during the initial 3 months following ACL-reconstruction. That study demonstrated a knee extensor torque ratio of approximately 0.3 two weeks following ACL-reconstruction with bone-patella tendon-bone graft and approximately 0.5 six weeks after surgery. The most commonly used tool that is reliable in assessing single-joint muscle strength is isokinetic dynamometry [36, 48]. Because seated knee extension in open kinetic chain is the test setup for single-joint muscle strength measurement of quadriceps, the lack of muscle function assessments during the initial 3 months following ACL-reconstruction may be due to concerns about the risk of elongating the ACL graft [31]. In contrast, there may not be the same concern regarding the leg extensor power measurement because that is a multijoint measurement conducted in closed kinetic chain.

The present results indicate that high-intensity resistance training appears to be safe. One concern could be that open kinetic chain, high-intensity knee extensor resistance training would cause anterior knee pain [47], but we had no reports of increased anterior knee pain in the HRT-group. Similarly, Morrissey et al. [47] detected no difference in anterior knee pain between knee extensor and leg extensor resistance training (3×20 RM) in the early period (2–6 weeks after surgery) after ACL-reconstruction with bone-patella tendon-bone graft. The fact that HRT resulted in a greater improvement in leg extensor muscle power compared with

TABLE 4: Results self-reported data before surgery and 7 and 20 weeks after the ACL-reconstruction.

	Presurgery		7 weeks after surgery		20 weeks after surgery	
	HRT	LRT	HRT	LRT	HRT	LRT
Lysholm score	70 (47–81)	63 (57–80)	60 (49–67)	62 (61–74)	80 (66–84)	80 (74–85)
Tegner score	3 (2–5)	2 (2–4)	2 (2–2)	2 (2–2)	4 (2–5)	3 (2–4)
KOOS						
Pain	80 (64–94)	81 (72–92)	69 (63–75)	75 (64–78)	83 (65–93)	81 (78–89)
Symptoms	89 (68–96)	75 (64–89)	64 (57–80)	54 (46–64)	86 (68–96)	79 (68–89)
ADL	93 (78–96)	89 (85–97)	78 (73–88)	85 (72–91)	91 (83–98)	93 (90–96)
Sport/rec	70 (43–75)	70 (40–85)	35 (20–40)	35 (25–55)	60 (43–73)	55 (45–70)
QOL	44 (38–56)	50 (38–50)	44 (28–50)	44 (38–56)	50 (34–66)	50 (44–63)

Results are presented as median and interquartile range.

HRT: high-intensity resistance training; LRT: low-intensity resistance training; KOOS: knee injury and osteoarthritis outcome score with subscales (0: extreme symptoms, 100: no symptoms): pain, other symptoms, ADL: function in daily living, sport/rec: function in sport and recreation, and QOL: knee-related quality of life.

LRT in our study suggests that this type of training can be recommended in future ACL rehabilitation programs.

Most likely, the superior gains following HRT versus LRT appeared as the result of more marked adaptations in neuromuscular function [28, 49] and/or a greater muscle hypertrophy response [50, 51]. In support of this notion, it has been demonstrated that heavy resistance exercise is highly effective of eliciting enhanced neuromuscular activity [28, 52] and skeletal muscle growth [50, 51]. These effects are less pronounced following resistance training using low external loads [53]. Both groups performed leg press and hamstrings exercises, which only differed in training intensity. In contrast, the HRT-group performed seated knee extension exercise and the LRT-group performed heel raises in the standing position. Because extensor muscles of the knee, hip, and ankle all contribute to the results in leg extensor power [39] it cannot be excluded that both the seated knee extension exercise and the heel raises in the standing position may have influenced the results. On the other hand, the test movements (Nottingham Power Rig procedures) were not employed during training in any of the two intervention groups, resulting in only minimal learning effects.

According to the recommendations from American College of Sports Medicine, two general loading strategies should be used for improving power: (1) strength training and (2) use of low intensity (0–60% of 1RM) performed at a fast contraction velocity [28, 29]. For safety reasons our participants performed the contractions at a low speed because the weight training started fairly soon after surgery. In healthy adults, low-intensity resistance training with slow movement has not convincingly been shown to improve power or function [28]. It could thus be speculated that the faster improvement in power in the HRT-group may have been due to the heavier loads lifted [49]. This finding is supported by a study on endurance runners [49] which showed that 8 weeks of heavy strength training was more beneficial in improving neuromuscular characteristics than muscle endurance exercise and in particular contributed to improvements in high-intensity running performance. Yet, we had expected a greater between-group difference in muscle power following the training period but the effective

period with HRT (load 8 RM) lasted only 6 weeks and this period was probably too short to elicit very marked differences in outcome. On the other hand, a recent study [54] found equal improvements in knee extensor maximal power output, rate of force development, and hypertrophy after 10 weeks of unilateral knee extension resistance training with low intensity (30% of 1 RM) lifted to failure versus high intensity (80% of 1 RM) lifted to failure. Finally, in the late phase of the 20-week rehabilitation program all participants performed plyometric training as part of the group-based program, and this type of training may have had a positive effect on leg extension muscle power [55].

Our second hypothesis was not confirmed since HRT did not appear to regain knee function as evaluated by the hop tests faster. It could be argued that the period with high-intensity resistance exercise was not long enough (load 8 RM, 14 to 20 weeks after surgery) and that a longer training period would have been needed to ensure transferability from increased muscle function to improvement in the hop tests. Further, the plyometric training, which was performed in both groups, may have contributed to this lack of between-group differences [55]. Moreover, the hop test is more complex than the Leg Extensor Power Rig test as it requires power, balance, and coordination. Finally, fear avoidance may have played a role [56]. The relationship between single-leg hop capabilities, muscle function, and anterior knee joint laxity in conjunction with fear of movement and reinjury has not been investigated in patients following ACL-reconstruction [56]. According to the postoperative regimen at our hospital participation in knee-demanding sports was not allowed until 9 to 12 months after surgery. Therefore, fear of painful reinjury may have caused the patients to avoid behaviours that would potentially increase the risk of reinjury.

The mechanical stability of the knee increased as a result of the ACL-reconstruction, which is consistent with results of previous studies [57, 58]. Importantly, our results suggest that neither low-intensity nor high-intensity resistance training has an adverse effect on knee joint stability since there were no significant changes in knee laxity during the weight training period.

Regarding self-reported outcomes there were no significant differences between the groups. Both groups increased in Lysholm score from before surgery to 20 weeks after surgery (Table 4). The presurgery values correspond to those documented in patients with abnormal or severely abnormal overall knee function while the values 20 weeks after surgery correspond to normal or nearly normal overall knee function [43].

In contrast, results in all KOOS subscales were the same before surgery and 20 weeks after surgery (Table 4). Roos et al. [42] showed a large effect size for the KOOS instrument 6 months after surgery and the largest effect size for the subscales “function in sport and recreation” and “knee-related quality of life” [42]. However, because our participants were not allowed to participate in knee-demanding sports 6 months after surgery restrictions in sports may have resulted in lower scores in the subscales “function in sports and recreation” and “knee-related quality of life.”

4.1. Strength and Limitations. The strength of our study is that we were able to document the substantial decline in muscle power during the first 7 weeks after surgery and the subsequent recovery in muscle power of the ACL-reconstructed limb by means of the Leg Extensor Power Rig. This measuring equipment has not previously been used to test muscle function after ACL injury or ACL-reconstruction. However, the Nottingham Power Rig has been used to evaluate muscle function in healthy people, aged 20–86 [39, 59], and in a wide range of individuals with known musculoskeletal pathologies/deficits, including geriatric patients after proximal femoral fracture [60]. The assessment is not time consuming; it is easy and safe to perform for all age groups and levels of physical capacity [39], while at the same time being reproducible (CV = 9–13%) in healthy people, aged 20–86 [39]. The present results demonstrate that this method can discriminate between muscle power in the ACL limb and the healthy limb up to 20 weeks after surgery as well as detect training induced changes in this parameter over time. This implies that the Leg Extensor Power Rig may be used in the early phase of the rehabilitation program to assess the status and progress the rehabilitation after ACL tear or -reconstruction. However, the reliability and agreement as well as the validity of the leg extensor power measurement need to be determined in people with ACL injuries.

Our study has some limitations. First, we had a high number of dropouts, which means that we did not reach the desired number of patients in each group. This weakens the statistical power of our results. On the other hand, a small sample size would probably make it more difficult to document a longitudinal effect of training. The participants who dropped out had greater preoperative knee laxity in the ACL injured knee compared to those who completed the rehabilitation program. Since there were no differences between the groups when the strength training started, we do not think that the difference in laxity before surgery is of significant importance. Further, the HRT-group had significantly longer time between injury and surgery than the

LRT-group. This could have resulted in more degenerative changes, that is, meniscus and cartilage damage in the HRT-group, but no between-group differences in cartilage and meniscus damage were reported. In addition, the weight training in the two groups did not consist of exactly the same exercises and was not entirely matched for total training volume. The limitations mentioned imply that our results may not be generalizable to all patients going through an ACL-reconstruction.

5. Conclusion

The present data indicate that high-intensity resistance training as part of early rehabilitation after ACL-reconstruction may contribute to a faster recovery of leg extension muscle power compared with low-intensity resistance training without introducing any adverse effect on knee joint stability. Most likely, the accelerated/amplified gains observed with high-intensity resistance training were caused by more marked neuromuscular adaptations and/or greater muscular regrowth induced by this training modality.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

High-Intensity Intermittent Swimming Improves Cardiovascular Health Status for Women with Mild Hypertension

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To test the hypothesis that high-intensity swim training improves cardiovascular health status in sedentary premenopausal women with mild hypertension, sixty-two women were randomized into high-intensity ($n = 21$; HIT), moderate-intensity ($n = 21$; MOD), and control groups ($n = 20$; CON). HIT performed 6–10 \times 30 s all-out swimming interspersed by 2 min recovery and MOD swam continuously for 1 h at moderate intensity for a 15-week period completing in total 44 ± 1 and 43 ± 1 sessions, respectively. In CON, all measured variables were similar before and after the intervention period. Systolic BP decreased ($P < 0.05$) by 6 ± 1 and 4 ± 1 mmHg in HIT and MOD, respectively. Resting heart rate declined ($P < 0.05$) by 5 ± 1 bpm both in HIT and MOD, fat mass decreased ($P < 0.05$) by 1.1 ± 0.2 and 2.2 ± 0.3 kg, respectively, while the blood lipid profile was unaltered. In HIT and MOD, performance improved ($P < 0.05$) for a maximal 10 min swim ($13 \pm 3\%$ and $22 \pm 3\%$), interval swimming ($23 \pm 3\%$ and $8 \pm 3\%$), and Yo-Yo IE1 running performance ($58 \pm 5\%$ and $45 \pm 4\%$). In conclusion, high-intensity intermittent swimming is an effective training strategy to improve cardiovascular health and physical performance in sedentary women with mild hypertension. Adaptations are similar with high- and moderate-intensity training, despite markedly less total time spent and distance covered in the high-intensity group.

1. Introduction

Arterial hypertension is associated with cardiovascular morbidity and mortality, and it is well known that the risk of arterial hypertension is markedly elevated by obesity and an inactive lifestyle [1, 2]. Additionally, there is strong evidence that exercise training lowers arterial blood pressure, improves aerobic fitness, and counteracts several other cardiovascular risk factors related to increased morbidity in patients with

mild to moderate hypertension [3, 4], but it is still debated whether the magnitude of training response is related to exercise mode and the type of training performed.

The vast majority of studies investigating the relationship between exercise training and cardiovascular health responses have applied running, cycling, or team sports participation as the training intervention [5–7], whereas few have examined the effects of different aquatic exercise regimes [8–10]. Swimming may be considered a good choice

of training especially for obese middle-aged and elderly individuals because it involves minimum weight-bearing stress, which may reduce the risk of injury. In addition, swimming engages the upper body musculature where the potential for metabolic adaptation can be hypothesized to be larger than in the postural musculature. However, little information is available concerning the effects of regular swimming exercise training on the cardiovascular health profile. Nualnim and coworkers [10] demonstrated that 12 wks of regular 15–45 min continuous moderate-intensity swimming lowered systolic blood pressure (SBP) by 9 mmHg in adults older than 50 yrs with mild hypertension. The swimming exercise training also resulted in a 21% increase in carotid artery compliance, as well as improvement in flow-mediated dilation and cardiovagal baroreflex sensitivity [10]. However, no studies have compared different swim training regimes in sedentary women suffering from mild to moderate arterial hypertension.

Lack of time is a common explanation why people fail to participate continuously in traditional exercise regimes based on prolonged session of moderate-intensity training. Therefore, it is of interest to explore the health effects of short-duration exercise training protocols. Numerous findings indicate that brief high-intensity training appears to be efficient in improving aerobic fitness and other physiological adaptations of importance for the cardiovascular health status in untrained individuals [6, 7, 11]. Moreover, short-term sprint training apparently provoked similar muscle metabolic and exercise performance adaptations as prolonged submaximal training protocols [12, 13]. These studies challenge the pronouncement by sports medicine authorities that 150–250 min of moderate-intensity exercise per week is required to maintain a healthy lifestyle [14, 15] and support the idea that 75 min of vigorous exercise may be sufficient [16]. For example, Nybo et al. [6] found differences in the adaptive response within several indicators of cardiovascular health to short-duration high-intensity intermittent running compared to prolonged submaximal continuous running, including more pronounced effects on maximal oxygen uptake for the high-intensity training group. This study was performed on sedentary men, while Metcalfe et al. [17] demonstrated marked improvements in aerobic capacity and metabolic health after intensified cycling in sedentary participants of both genders. However, it is currently unclear to what extent women respond to submaximal prolonged versus short-term high-intensity swim training. Gender differences have been shown to be present within a range of physiological adaptations to exercise training [4, 18]. For example, women appear to display smaller reductions in blood pressure after exercise training interventions in comparison to their male counterparts [4, 5, 19]. It is therefore of importance to investigate the effect of two types of swimming exercise training on the cardiovascular disease risk profile in sedentary women with mild to moderate hypertension.

Thus, the objective of the present study was to test the hypothesis that high-intensity swim training is an efficient strategy to reduce blood pressure and improve the cardiovascular health profile in sedentary premenopausal women with mild to moderate hypertension.

2. Materials and Methods

Sixty-two sedentary premenopausal women with mild to moderate arterial hypertension were recruited for the study. The subjects were selected among 262 volunteers based on training history, medication, blood pressure, and body mass index. A total of 83 participants were recruited. 62 took part in the present study and 21 were randomly assigned to a football group being part of another study [20]. In addition, the control group (20 participants) in the present study was also the controls in the above-mentioned study by Mohr et al. [20]. The study was approved by the ethical committee of the Faroe Islands as well as the Sport and Health Sciences Research Ethics Committee at the University of Exeter, Exeter, UK, and conducted in accordance with the Declaration of Helsinki (1964). After being informed verbally and in writing of the experimental procedures and associated risks, all participants gave their written consent to take part in the study.

2.1. Experiment Design. The study was designed as a randomized controlled trial. After initial testing of the 262 volunteers, 62 participants were enrolled in the present study based on selection criteria being a sedentary lifestyle for the last two years, mild hypertension (mean arterial pressure 96–110 mmHg), and a body mass index >25. Participants treated with adrenergic beta-antagonists were excluded. Participants using diuretics and ACE inhibitors ($n = 4$) were not excluded from the study, but none of the four subjects changed their medication during the intervention period. The participants were randomized into a high-intensity intermittent swimming training group (HIT: age 44 ± 2 (36–49) \pm SEM (range) yrs; height 164 ± 1 cm; weight 76.5 ± 1.9 kg; $n = 21$), a moderate-intensity continuous swimming group (MOD: age 46 ± 2 (38–48) yrs, height 165 ± 1 cm, weight 83.8 ± 4.3 kg; $n = 21$), and a control group (CON: age 45 ± 2 (35–48) yrs, height 166 ± 1 cm, weight 76.4 ± 2.6 kg; $n = 20$). The training groups took part in two types of swimming training with 3 training sessions per week for 15 wks, while CON had no training or lifestyle changes in the same period. There were no dropouts from the study, but one subject in the MOD group suffered from aquatic phobia and was therefore moved to CON. All subjects performed an intermittent swimming sprint test and an endurance swimming test, as well as an intermittent running test with heart rate recordings, and had their blood pressure, resting heart rate (RHR), body fat content, and blood cholesterol measured before and after the intervention. Finally, basic anthropometrical measurements were performed. The pre- and posttests were conducted in the same order. The postfitness tests were conducted 48–72 h after the last training session. The training was continued until the last measurement was obtained. The dietary intake was not controlled during the training period and the testing periods were not timed in relation to the menstrual cycle.

2.2. Training Intervention. The HIT participants completed in total 44 ± 1 (39–50) training sessions over the 15-week intervention period corresponding to 2.9 ± 0.1 (2.6–3.3) sessions per week. Every session lasted ~15–25 min (3–5 min

of effective swimming) and consisted of 6–10 30 s all-out free-style swimming (front crawl) intervals interspersed by 2 min of passive recovery after training principles previously described [21, 22]. In the first 6 wks of training the participants completed 6 intervals, the following 6 wks included 8 intervals, and the final 3 wks consisted of 10 all-out swimming intervals. The MOD group completed a total of 43 ± 1 (37–49) training sessions over 15 wks corresponding to 2.9 ± 0.1 (2.5–3.3) training sessions per week. All MOD training sessions lasted 1 h and consisted of continuous front crawl swimming where the participants were encouraged to swim as far as possible in every session. Five trained swimming coaches were present during all training sessions in order to give technical advice and control the intensity and duration of the training and to secure a safe training environment. Heart rate was measured during one training session in week 1 and one session in week 15 of the training intervention, and the swimming distance was noted in every session.

2.3. Blood Pressure and RHR Measurements. The participants reported to the hospital at 8:00 a.m. after an overnight fast and rested in a supine position for 2 h. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured according to standard procedures [23] using an automatic BP monitor (HEM-709; OMRON, IL, USA) once every 30 min over the 2 h resting period. The average of the four measurements was used as the test result. Mean arterial pressure (MAP) was calculated as $1/3 \text{ SBP} + 2/3 \text{ DBP}$. Resting HR was measured during the same time intervals as the BP recordings.

2.4. Resting Blood Sampling. A resting blood sample was collected under standardized conditions from an antecubital vein between 7:00 and 8:00 a.m. after an overnight fast using venipuncture technique. The blood was rapidly centrifuged for 30 s and analyzed by an automatic analyzer (Cobas Fara, Roche, France) using enzymatic kits (Roche Diagnostics, Germany) for determination of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels.

2.5. DXA Scanning. Whole-body body fat and lean body mass were evaluated by total body DXA scanning (Norland XR-800, Norland Corporation, Norway). The body was segmented in accordance with standard procedures to evaluate regional fat distribution [24], and all analyses were performed using Illuminatus DXA software (Norland Corporation, Norway). The effective radiation dose was $<0.2 \text{ mSv}$ per scan.

2.6. Exercise Performance Testing. The participants in HIT and MOD performed two front crawl swimming tests before and after intervention. To evaluate if the high-intensity training improved the ability to repeatedly perform high-intensity swimming more than moderate-intensity training, a repeated swimming sprint test (RSST) composed of $4 \times 25 \text{ m}$ sprinting starting every 60 s was performed. The participants were instructed to swim each 25 m as fast as possible. To evaluate if continuous training was more efficient in improving continuous swimming performance, a 10 min continuous

swimming test was performed. Swimmers were instructed to complete the largest possible swimming distance during the 10 min. Swim testing was performed in a 25 m pool at a water temperature of 26°C . To evaluate if the swim-training intervention improved exercise capacity in a land-based activity, all participants additionally completed a shuttle-run test. The Yo-Yo Intermittent Endurance test, level 1 (Yo-Yo IE1), was completed before and after the training period. The Yo-Yo IE1 test consists of $2 \times 20 \text{ m}$ shuttle runs interspersed by a 5 s recovery period consisting of $2 \times 2.5 \text{ m}$ jogging (see [25]). There is a gradual speed progression during the test, which is controlled by a CD player [26]. The participants run until the point of exhaustion defined as the second time they are unable to complete the $2 \times 20 \text{ m}$ runs at the required pace [25]. Maximum heart rate (HR_{max}) was determined during the test as previously described [25]. The preintervention test was performed within ten days of the first training and the postintervention test four days after the last training session. The tests were conducted indoor on a wooden surface at environmental temperatures between 18 and 20°C . The tests were preceded by a short warm-up period consisting of the first three of the $2 \times 20 \text{ m}$ shuttle runs, followed by a 2 min recovery period before the exhaustive test. Heart rate was measured continuously during the tests using Polar Vantage NV chest belt monitor weighing $\sim 100 \text{ g}$ (Polar Electro Oy, Kempele, Finland), and HR_{max} was determined as previously described [26]. The pre- and postintervention tests were conducted at the same time of day. All participants were familiarized to all test procedures prior to the experiment according to guidelines presented in Bradley et al. [26]. The participants were instructed to avoid exercise training and intake of alcohol the day prior to the testing and nutritional items rich in caffeine on the day of testing. In addition, the participants were also instructed to note the food intake and follow similar nutritional guidelines during the last 24 h before both test periods.

2.7. Hip and Waist Circumference and Body Weight. Hip and waist circumference was assessed as described by Kharal et al. [27]. Body mass was assessed by weighing the participant. The weighing was performed in the morning after an overnight fast using a platform scale (Ohaus, Germany).

2.8. Statistical Analyses. Data are presented as means \pm SEM. Between- and within-group data were evaluated both by two-factor mixed ANOVA design and with one-way ANOVA on repeated measurements. When a significant interaction was detected, data were subsequently analyzed using a Newman-Keuls post hoc test. Significance level was $P < 0.05$.

3. Results

3.1. Heart Rate and Distance Covered during Training. Average mean and peak HR during HIT training in the first and last weeks of the intervention was 158 ± 5 and $176 \pm 2 \text{ bpm}$, respectively, corresponding to 85.5 ± 1.1 and $95.3 \pm 1.1\%$ HR_{max} , respectively, which was higher ($P < 0.05$) than average values in MOD (132 ± 4 and $144 \pm 3 \text{ bpm}$ equivalent

to 72.5 ± 0.9 and $79.1 \pm 1.0\%$ HR_{max}). No differences in heart rate between the first and last weeks of training were detectable within either training group. In HIT the average swim distance per session during the first week was 131 ± 7 m and increased ($P < 0.05$) to 269 ± 10 m during the last training week. Average swim distance per swimming interval increased ($P < 0.05$) by $28 \pm 6\%$ from the first to the last training week. In MOD the average swim distance per session was 1177 ± 41 m during the first training week and was increased ($P < 0.05$) to 1787 ± 35 m ($52.8 \pm 3.2\%$) during the last training week.

3.2. Blood Pressure and Resting Heart Rate. Prior to the intervention period, SBP and DBP were 138 ± 4 and 86 ± 3 mmHg in HIT, 142 ± 4 and 87 ± 2 mmHg in MOD, and 134 ± 4 and 82 ± 2 mmHg in CON, respectively, with no differences between groups. In HIT, SBP decreased ($P < 0.05$) by 6 ± 1 mmHg ($4 \pm 1\%$) during the 15 wk intervention period (Figure 1), while the MOD group displayed a decrease ($P < 0.05$) of 4 ± 1 mmHg ($3 \pm 1\%$) in SBP. DBP was similar before and after intervention for HIT and MOD (Figure 1). No significant changes took place in neither SBP nor DBP in CON (0 ± 0 and 0 ± 0 mmHg, Figure 1). MAP was 103 ± 4 and 99 ± 2 mmHg before training in HIT and CON, respectively, and tended ($P = 0.06$) to decrease (3 ± 1 mmHg, $3 \pm 1\%$) after intervention in HIT, with no changes in MOD or CON (-1 ± 0 and 0 ± 0 mmHg, Figure 1). Sixteen of the twenty-one subjects in HIT experienced a decline in MAP during the intervention period, with corresponding numbers in MOD being thirteen out of twenty-one and eleven out of twenty in CON.

Resting HR decreased ($P < 0.05$) by 5 ± 1 bpm over 15 wks both in HIT (76 ± 2 to 71 ± 2 bpm) and MOD (78 ± 3 to 73 ± 2 bpm), whereas it was not significantly altered in CON (77 ± 2 and 74 ± 2 bpm).

3.3. Body Fat, Lean Body Mass, and Anthropometry. Total body fat percentage was 43.1 ± 1.1 , 44.1 ± 1.2 , and $41.0 \pm 1.2\%$ before training in HIT, MOD, and CON, respectively, and decreased ($P < 0.05$) by a similar magnitude to 41.4 ± 1.2 and $42.1 \pm 1.0\%$ in HIT and MOD, respectively, with no change in CON ($41.5 \pm 1.1\%$). Total fat mass decreased by 1.1 ± 0.2 and 2.2 ± 0.3 kg ($P < 0.05$) in HIT and MOD, respectively, during the 15 wks but remained similar in CON (Figure 2). Lean body mass increased ($P < 0.05$) by 1.7 ± 0.3 and 1.3 ± 0.3 kg in HIT and MOD, respectively, with no significant changes in CON (Figure 2). Hip circumference was lowered ($P < 0.05$) in MOD (108 ± 2 to 105 ± 2 cm) but not in HIT (104 ± 1 to 103 ± 2 cm) and CON (104 ± 1 to 103 ± 1 cm). Waist circumference declined ($P < 0.05$) in HIT (86 ± 2 to 83 ± 2 cm) and MOD (94 ± 3 to 89 ± 3 cm) but was stable in CON (84 ± 2 and 82 ± 2 cm). Total body mass was lowered ($P < 0.05$) over 15 wks in HIT (76.5 ± 1.9 to 75.9 ± 2.1 kg) and MOD (83.8 ± 4.3 to 82.4 ± 4.0 kg), but remained similar in CON (76.4 ± 2.6 and 77.3 ± 2.2 kg) (Figure 2).

3.4. Plasma Cholesterol and Triglycerides. Total plasma cholesterol was 5.6 ± 0.2 , 6.0 ± 0.2 , and 5.3 ± 0.2 mmol·L⁻¹ before the training intervention in HIT, MOD, and CON,

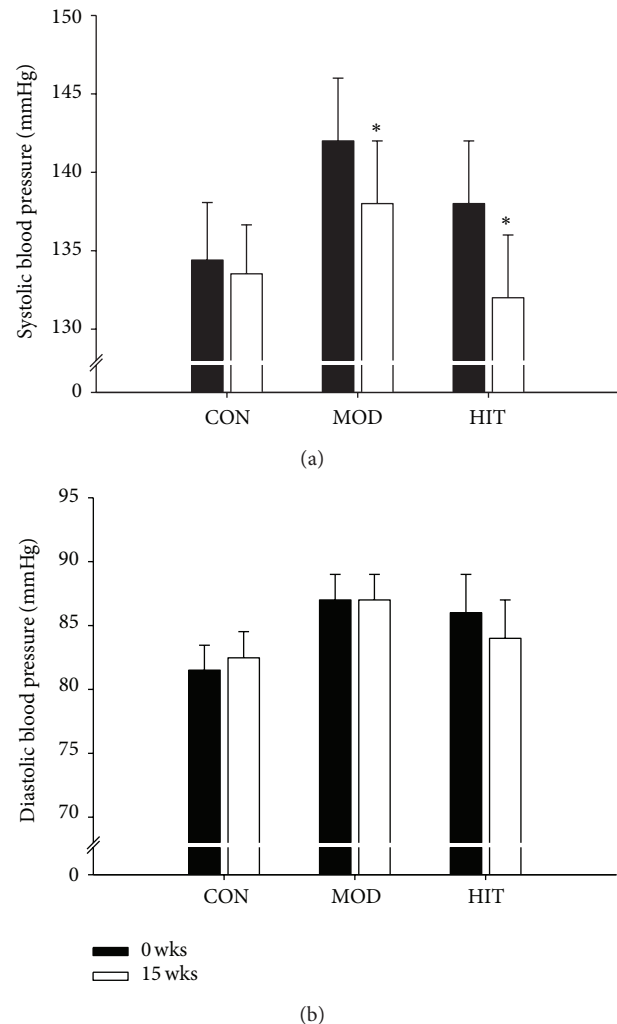


FIGURE 1: Systolic and diastolic blood pressure before and after 15 wks with thrice-weekly training sessions of high-intensity swimming (HIT) and moderate-intensity swimming (MOD) in comparison to an inactive control group (CON). Data are presented as means \pm SEM. # denotes significant within-group differences. * denotes significant difference between the training groups and CON.

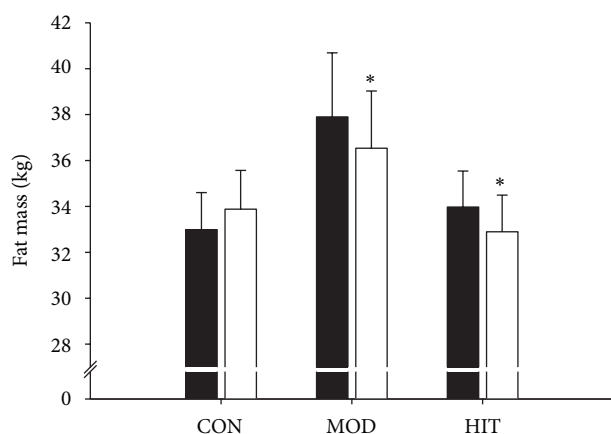
respectively, and was similar after the intervention period (Table 1). HDL and LDL cholesterol was 1.4 ± 0.1 and 3.7 ± 0.2 , 1.4 ± 0.1 and 3.9 ± 0.2 , and 1.4 ± 0.1 and 3.5 ± 0.2 mmol·L⁻¹ before training in HIT, MOD, and CON, respectively, and was unchanged after the intervention period (Table 1). Plasma triglyceride was 1.1 ± 0.1 , 1.4 ± 0.1 , and 1.0 ± 0.1 mmol·L⁻¹ in HIT, MOD, and CON before training, but was unchanged after the training intervention (1.0 ± 0.1 , 1.3 ± 0.2 , and 1.3 ± 0.2 mmol·L⁻¹).

3.5. Performance Testing. Before the training period, HIT and MOD covered 306 ± 15 and 305 ± 16 m, respectively, during the 10 min maximal swim. After the training period, performance was increased ($P < 0.05$) in HIT and MOD by $13 \pm 3\%$ and $22 \pm 3\%$, respectively, resulting in a

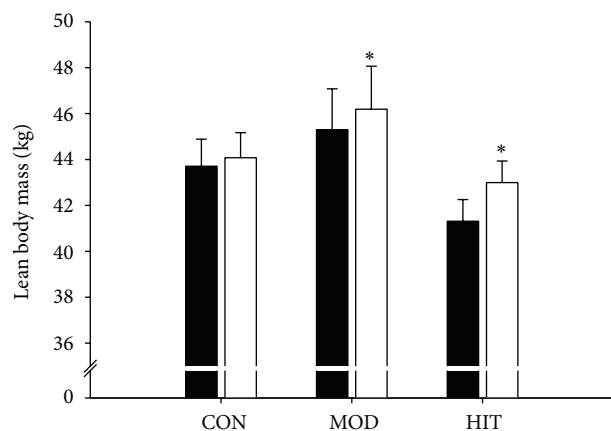
TABLE 1: Plasma total, HDL, and LDL cholesterol ($\text{mmol}\cdot\text{L}^{-1}$) before and after a 15 wks intervention period in HIT, MOD, and CON.

	Total cholesterol		HDL		LDL	
	Before	After	Before	After	Before	After
HIT	5.6 ± 0.2	5.5 ± 0.2	1.4 ± 0.1	1.4 ± 0.1	3.7 ± 0.2	3.6 ± 0.2
MOD	6.0 ± 0.2	5.8 ± 0.3	1.4 ± 0.1	1.5 ± 0.1	3.9 ± 0.2	3.8 ± 0.3
CON	5.3 ± 0.2	5.4 ± 0.2	1.4 ± 0.1	1.3 ± 0.1	3.5 ± 0.2	3.4 ± 0.2

Data are expressed as means \pm SEM.



(a)



(b)

FIGURE 2: Changes in body composition, including fat mass, lean body mass, and total body weight after 15 wks with thrice-weekly training sessions of high-intensity swimming (HIT) and moderate-intensity swimming (MOD) in comparison to an inactive control group (CON). Data are presented as means \pm SEM. * denotes significant difference between the training groups and CON.

total distance of 342 ± 14 m and 368 ± 15 m (Figure 4(a)). The improvement in MOD tended ($P = 0.07$) to be higher than in HIT. Mean accumulated swimming time in the 4×25 m repeated sprint test was 153 ± 9 and 141 ± 5 s in HIT and MOD, respectively, before the intervention. After training, accumulated swimming time was reduced ($P < 0.05$) in both

groups by 23 ± 3 and $8 \pm 3\%$, respectively, reaching 116 ± 7 and 129 ± 6 s. HIT reduced their accumulated swimming time more ($P < 0.05$) than MOD (Figure 4(b)).

Yo-Yo IE1 performance before intervention was $413\text{--}458$ m in the three groups ($P > 0.05$) and increased ($P < 0.05$) similarly by 58 ± 5 and $45 \pm 4\%$ after training in HIT and MOD, respectively, with no changes in CON (Figure 3(a)). HR after the initial five 2×20 m runs was 92.5 ± 1.1 , 94.1 ± 1.0 , and $92.3 \pm 1.0\%$ HR_{max} before training in HIT, MOD, and CON, respectively, but was reduced ($P < 0.05$) similarly by 4.5 ± 0.5 and $3.5 \pm 0.4\%$ after intervention in HIT and MOD, respectively (88.0 ± 1.4 and $90.6 \pm 1.2\%$ HR_{max} , resp.) whilst HR remained similar in CON ($93.2 \pm 0.7\%$ HR_{max} ; Figure 3(b)). No difference was detected in shuttle-run performance or heart rate response between HIT and MOD.

4. Discussion

The present study is the first to examine if two different types of swim training can improve the cardiovascular health profile and land-based exercise capacity in sedentary premenopausal women with mild to moderate hypertension. The principal findings reveal that both short-term intermittent high-intensity and prolonged moderate-intensity swim training reduced systolic blood pressure and improved both water and land-based exercise capacities. Because the HI group only covered $\sim 11\text{--}15\%$ of the total mileage and spent one-third of time on training compared to the moderate-intensity training group, high-intensity intermittent training appears to be a time-efficient alternative to traditional recreational training regimes in untrained individuals.

The present findings support that swim training appears to have a high potential in the treatment of patients with arterial hypertension, which is supported by others applying aquatic training protocols [8–10, 28]. For example, similar decreases in blood pressure were reported by Tanaka et al. [28] and Nualnim and coworkers [10] demonstrated that 12 wks of regular swim training lowered SBP by 9 mmHg in adults older than 50 yrs with mild hypertension. In addition, the swim exercise training also produced a 21% increase in carotid artery compliance, as well as improvements in flow-mediated dilation and cardioagal baroreflex sensitivity [10]. In addition, in a cross-sectional study, middle-aged swimmers had a lower carotid systolic blood pressure and carotid pulse pressure than sedentary controls. Moreover, carotid arterial compliance was higher and β -stiffness index was reported to be lower in the swimmers in comparison

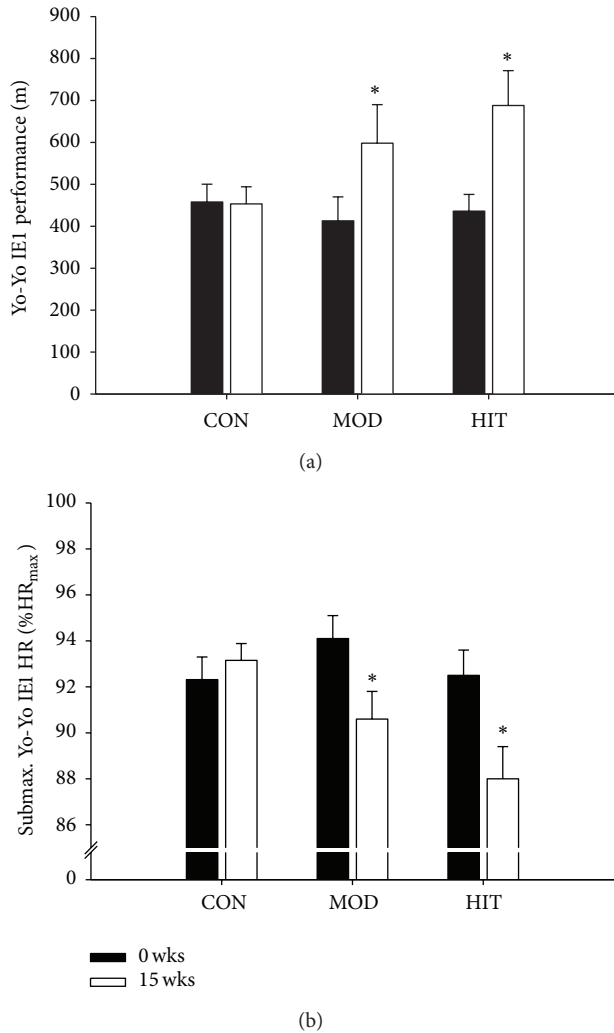


FIGURE 3: Yo-Yo Intermittent Endurance level 1 performance (a) as well as heart rate after controlled intermittent submaximal exercise (%HR_{max}, (b)) before and after 15 wks with thrice-weekly training sessions of high-intensity swimming (HIT) and moderate-intensity swimming (MOD) in comparison to an inactive control group (CON). Data are presented as means \pm SEM. * denotes significant difference between the training groups and CON.

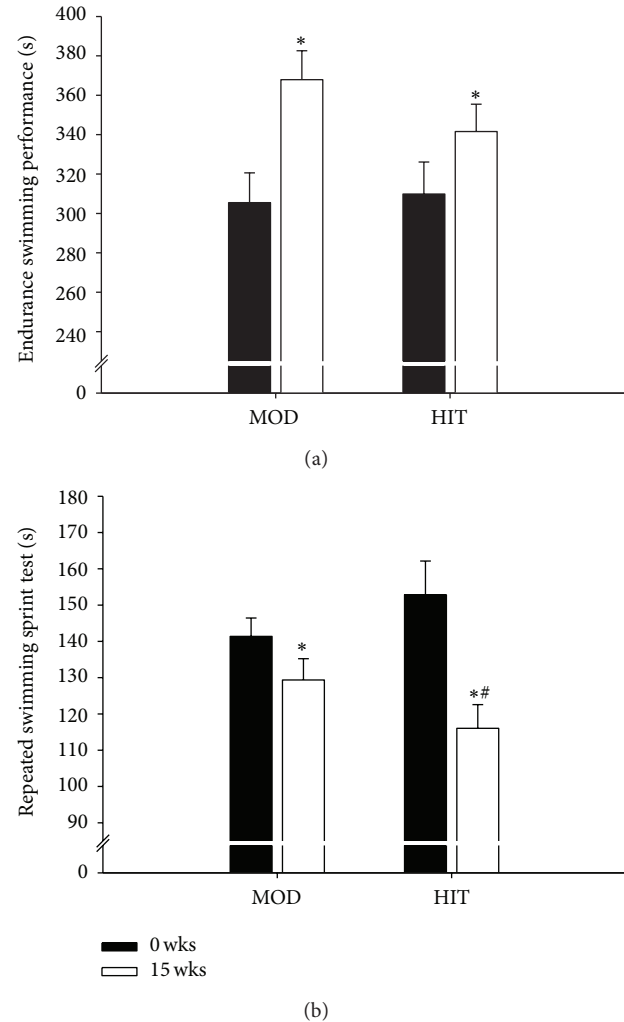


FIGURE 4: Endurance swimming performance (a) and repeated swimming sprint time (b) before and after 15 wks with thrice-weekly training sessions with high-intensity swimming (HIT) and moderate-intensity swimming (MOD) in comparison to an inactive control group (CON). Data are presented as means \pm SEM. * denotes significant difference between the training groups and CON. # denotes significant differences between HIT and MOD.

to the controls [29]. Thus, both intermittent high-intensity and continuous moderate-intensity swimming can be recommended for adults with mild hypertension.

In some review articles it is suggested that low-to-moderate-intensity exercise regimes are more efficient than protocols encompassing high-intensity exercise [30]. However, in the present study both training groups' SBP was lowered by 3-4%, which confirms findings in untrained men in their mid-thirties performing intense intermittent and continuous moderate-intensity running [6]. In the study by Nybo et al. [6], SBP was lowered in both training groups, but only DBP declined in the continuous moderate-intensity group, while mean arterial pressure (MAP) declined after both types of training. In the present study DBP was unchanged in both swim training groups, and MAP tended ($P = 0.06$) to decline

only in the high-intensity training group with 76% of the participants demonstrating a reduction. Thus, the discrepancy between findings by Nybo et al. [6] and the present study may relate to the differences in training mode, since exercise in a supine position may provide a different training stimulus to cardiovascular parameters compared to upright exercise modes such as running due to the differences in ventricular volumes [31]. Moreover, gender differences have been shown to be present within a range of physiological adaptations to exercise training [4, 17]. Nybo et al. [6] used male participants and women seem to display smaller reductions in blood pressure after exercise training interventions in comparison to their male counterparts [4, 5, 19]. In contrast Ishikawa et al. [32] demonstrated that the gender did not influence the efficacy of physical activity for lowering elevated blood pressure.

In a recent study by Rocha et al. [33] isogenic rats were exposed to swim training at low, moderate, and high intensities and large morphological alterations in the cardiac myocytes occurred after high-intensity training in comparison to low and moderate intensities. These findings are in line with several recent review papers supporting that high-intensity training markedly reduced arterial blood pressure [18, 19, 34]. In addition, supportive of this notion are several studies on cardiovascular effects of recreational football training from our laboratory on sedentary men [5, 19, 23] and women [35, 36]. Thus, the rapid acceleration of heart rate and stroke volume during square-wave transitions from low- to high-intensity exercise as performed in the high-intensity training group in the present study may be an important stimulus to blood pressure reduction. This suggestion is backed up by the similar responses observed in the two training interventions despite large differences in training volume.

In the present study total fat mass was reduced and lean body mass increased in both training groups. In the aforementioned study by Nybo et al. [6] with untrained men high-intensity running did not change fat mass or fat oxidation during submaximal exercise. In contrast, the moderate-intensity running group displayed a reduction in fat mass as in the present study. Studies by Tjønnå et al. [7, 37] and Schjerve et al. [38] compared “isocaloric” high-intensity and moderate-intensity training and found major advantages of the high-intensity training regimes. However, in these studies the overall energy turnover was matched in contrast to the present study. Therefore, it may be surprising that the reduction in fat mass was not different between the HIT and MOD interventions despite the large difference in total energy turnover. The caloric intake was not controlled in the present study, which may have affected the body fat adaptations. For example, it has recently been demonstrated that appetite regulating variables such as leptin are affected by high-intensity training [39]. Additionally, the findings in the present study are supported by others showing marked decreases in body fat content after high-intensity training [40–42].

No changes were observed in blood lipid profile in the present study, which is in contrast to findings by others demonstrating that prolonged moderate-intensity running reduces total/HDL-cholesterol ratio and elevates fat oxidation during exercise in contrast to brief intense interval training [6]. It is suggested that changes in blood lipid profile relates to changes in fat mass [43], and in the present study no statistical differences were evident between the reduction in body fat between the two interventions, which may partly explain the similar blood lipid responses. One explanation for the above-mentioned discrepancy might be that some of the participants in the present study had normal plasma cholesterol levels prior to the intervention. If the participants who had total cholesterol levels lower than $5.5 \text{ mmol}\cdot\text{L}^{-1}$ were excluded from the statistical analysis, there was a significant reduction in total cholesterol in the MOD training group and a tendency ($P < 0.06$) to a reduction in HIT (data not shown), indicating that women with high plasma cholesterol levels are more likely to respond to exercise.

The improved performance after high-intensity as well as moderate-intensity swimming conducted in the present study may be related to an improved physiological capacity, improved swimming technique, or both. The rather large ~50% improvement in land-based shuttle-run performance observed in the two swim-training groups, but not in the control group, strongly indicates that physiological adaptations are a major contributor for the augmented exercise capacity observed during both shuttle runs and swim tests. This is further supported by the ~4% heart rate reduction observed after the initial five $2 \times 20 \text{ m}$ runs indicating improved aerobic capacity. Previously, the possible transfer effect between swim training and land-based activity has been neglected. This is largely because increases in maximal oxygen uptake after swim training appear to be specific for that exercise modality as observed in monozygotic twins [44] and an observation of unchanged running VO_2max , despite increased swimming VO_2max in elite swimmers after 9 months of intense training [9, 45]. However, shuttle-run performance is not strongly correlated to VO_2max [46, 47] and the current observation suggests that possible beneficial health adaptations obtained after swim training also translate into improved land-based exercise capacity. However, it also appears likely that a technical improvement may have occurred during the swim training. It can be speculated that the much higher total distance covered by the MOD group caused greater technical improvements than in the HIT group and that this is the reason for the tendency to a larger performance gain in the 10 min swim test of the MOD group. The larger improvement observed for the HIT than MOD group in repeated sprint swimming ability could be related to more specific motor learning leading to larger improvements in sprint technique in this group but could also be due to metabolic and physiological adaptations specific to sprinting. For example, high-intensity training is known to recruit more fast type II muscle fibres [48, 49] which could have yielded greater muscle hypertrophy and more pronounced enzymatic adaptations in type II fibres for the high-intensity group compared to the moderate-intensity training group [21]. Physiological adaptations that would favor improvements in intense short-duration exercise performance such as in the interval sprint test may be part of the explanation for the greater effect on sprint performance in the high-intensity swimming group (23 versus 8%). However, these suggestions remain speculative and warrant further investigation.

In conclusion, high-intensity intermittent swimming is a time-efficient and effective training method and improves cardiovascular health and physical performance in sedentary, premenopausal women with mild hypertension. Adaptations are similar with high- and moderate-intensity training, despite less total time spent and distance covered in the high-intensity group.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Resistance Training and Testosterone Levels in Male Patients with Chronic Kidney Disease Undergoing Dialysis

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Background. We investigated serum testosterone and insulin-like growth factor 1 (IGF-1) levels' associations with muscle fibre size and resistance training in male dialysis patients. **Methods.** Male patients were included in a 16-week control period followed by 16 weeks of resistance training thrice weekly. Blood samples were obtained to analyse testosterone, luteinizing hormone (LH), IGF-1, and IGF-binding protein 3. Muscle fibres' size was analysed in biopsies from *m. vastus lateralis*. **Results.** The patients' testosterone levels were within the normal range at baseline ($n = 20$) (19.5 (8.2–52.1) nmol/L versus 17.6 (16.1–18.0), resp.) whereas LH levels were higher (13.0 (5.5–82.8) U/L versus 4.3 (3.3–4.6), $P < 0.001$, resp.). IGF-1 and IGF-binding protein 3 levels were higher in the patients compared with reference values (203 (59–590) ng/mL versus 151 (128–276), $P = 0.014$, and 5045 (3370–9370) ng/mL versus 3244 (3020–3983), $P < 0.001$, resp.). All hormone levels and muscle fibre size ($n = 12$) remained stable throughout the study. Age-adjusted IGF-1 was associated with type 1 and 2 fibre sizes ($P < 0.05$). **Conclusion.** Patients' total testosterone values were normal due to markedly increased LH values, which suggest a compensated primary insufficiency of the testosterone producing Leydig cell. Even though testosterone values were normal, resistance training was not associated with muscle hypertrophy. This trial is registered with ISRCTN72099857.

1. Introduction

Endogenous testosterone and insulin-like growth factor 1 (IGF-1) are important factors in muscle anabolism in terms of stimulating muscle protein synthesis and inhibiting protein breakdown [1–3]. Thus, appropriate levels of anabolic hormones, as well as their function, are important for the avoidance of muscle atrophy, as well as the induction of muscle hypertrophy in relation to resistance training.

In male patients who undergo dialysis due to chronic kidney disease (CKD), serum testosterone levels are usually below, or in the low normal range, whilst luteinizing hormone

(LH) may be elevated [4–9]. Changes in androgen synthesis and metabolism develop even with moderate reductions in renal function and may be the result of primary hypogonadism and/or disturbances in the hypothalamic-pituitary axis [6]. Uraemic toxins, comorbidities, and several drugs are believed to be contributory to the observed changes, but the exact mechanism remains unclear [6].

In addition to altered testosterone levels, the growth hormone action of muscle mRNA IGF-1 is also impaired [10]. Low levels of these anabolic hormones in patients undergoing dialysis affect muscle protein balance negatively leading to a reduction in muscle strength and impaired

physical function [11, 12]. Whilst resistance training improves muscle strength in dialysis patients [13] the impact of testosterone levels on resistance training and muscle fibre size in these patients is generally unknown. We hypothesized that serum testosterone levels at baseline were decreased and associated with muscle fibre size in male patients undergoing dialysis. The aim of this study was to investigate association between resistance training and circulating levels of serum testosterone and IGF-1. The study was registered on <http://www.controlled-trials.com/> under number ISRCTN72099857.

2. Materials and Methods

2.1. Participants. This study population comprised male patients from a recent study of effects of resistance training in dialysis patients conducted by us, where the primary outcomes were changes in quality of life, physical performance, and both muscle power and strength [13]. The men were included from three dialysis centres in or around the capital of Denmark, to a control period of 16 weeks without any intervention followed by an intervention period of 16 weeks with resistance training. The inclusion criteria were age above 18 years, undergoing haemodialysis or peritoneal dialysis for more than three months, and the ability to participate in the training programme. Exclusion criteria were testosterone inhibiting medical treatment, insulin therapy, severe diabetic retinopathy, amputation of a lower limb, severe peripheral polyneuropathy, dementia, inability to speak Danish, and participation in other conflicting trials.

Data concerning renal disease and morbidity were obtained from case records, and levels of comorbidity were assessed using The Index of Coexistent Disease [14]. All tests were performed identically with regard to the dialysis procedure for each individual, before and after the control and training period to minimize interdialytic variation. Informed consent was obtained from all the patients and the local ethical committee approved this protocol (H-D-2008-124).

2.2. Intervention. The training programme has been described recently [13]. In brief, it consisted of supervised heavy load resistance training three times weekly for 16 weeks. The training began with 5 minutes of warm-up followed by up to 5 sets of leg press, leg extension, and leg curl. The rest period between each set was 60–90 seconds (the time between repetitions was not regulated). The programme was progressive and the load was increased according to increased muscle strength during the training period with a corresponding decrease in repetitions maximum from 15 to 6. Every set was performed to exhaustion.

2.3. Hormone Analyses. Blood samples were obtained in the morning hours after an overnight fast, a minimum of 18 hours after a training session. Serum was separated and kept frozen at -80° until analysis. Levels of testosterone, estradiol, LH, follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) were analysed by fluoroimmunochemical methods (Autodelfia, Wallac, Turku,

Finland) and inhibin-B by an enzyme-linked immunosorbent assay (Inhibin-B GenII, Beckman Coulter, USA). IGF-1 and insulin-like growth factor-binding protein 3 (IGF-BP3) levels were determined by a chemiluminescence based assay (Immulite 2000, Siemens Healthcare Diagnostics, Tarrytown, USA).

The intra- and interassay coefficient of variation (CV) for measurement of testosterone were <2% and 8%, respectively. For estradiol <4% and 8%, for both LH and FSH <2% and 6%, SHBG <5% and <9%, inhibin-B <3% and <13%, IGF-1 <2% and <12%, and IGF-BP3 <4% and 11%, respectively. The limits of detection (LODs) were testosterone 0.3 nmol/L, estradiol 70 pmol/L, LH 0.05 IU/L, FSH 0.05 IU/L, SHBG 0.23 nmol/L, inhibin-B 3 pg/mL, IGF-1 20 ng/mL, and IGF-BP3 100 ng/mL.

Free testosterone levels were calculated from total testosterone, SHBG, and albumin as described previously [15]. For the reference population we used a fixed albumin level of 43.8 g/L when free testosterone was determined. Hormone ratios were calculated by simple division.

2.4. Muscle Fibre Analyses and ATPase Histochemistry. The muscle fibre analyses and ATPase histochemistry have been described in detail elsewhere [13]. Muscle biopsies were obtained from the mid-region of *m. vastus lateralis*, mounted with Tissue-Tek (Sakura Finetek, Zoeterwoude, The Netherlands), and immediately frozen in isopentane cooled in liquid nitrogen and stored at -80°C until analysis. Serial sections (10 μm) from the muscle biopsy samples were cut and myofibrillar ATPase histochemistry was performed at pH 9.40 after preincubation at pH 4.37, 4.60, and 10.30 [16]. Computer image analysis was performed using an image analysis system (TEMA, Scan Beam ApS, Hadsund, Denmark). Fibre sizes were classified as major type 1 and type 2 [17]. Only truly horizontally cut fibres were included in the fibre size analyses.

2.5. Muscle Strength. Maximal voluntary knee extension was tested in an adjustable dynamometer chair (Good Strength, Metitur Ltd., Jyväskylä, Finland) at a knee angle of 60° from full extension. The patients were instructed to rapidly produce as much force as possible and hold it for 5 seconds. A minimum of three tests separated by 60 seconds of rest were conducted. For each subject the best performance with the highest value followed by a lower value was accepted as the result. The results were digitized into Newton (N) using the Good Strength software package (version 3.11. Metitur Ltd., Jyväskylä, Finland).

2.6. Blinding. The investigators who analysed the muscle morphology and hormone levels of the subjects were blinded to any other subject information, including the outcomes.

2.7. Statistical Analyses. Statistical analyses were carried out using IBM SPSS Statistics 19. The data distributions were tested using the Shapiro-Wilks test and Q-Q plots. Most residuals were found not to be normally distributed and statistical analyses were performed using nonparametric tests. The Wilcoxon Signed Ranks test was used to test for differences between baseline test and pretraining test (control period),

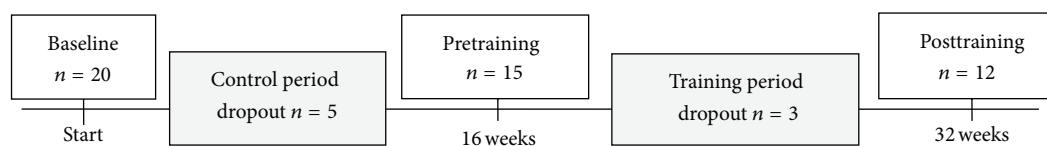


FIGURE 1: Study design and dropout.

between pretraining test and posttraining test (training period), and in-between periods. The Mann-Whitney test was used to compare the patients' data with data from the male reference population. The male reference population's hormone values were calculated using the patients' age as weights. The reference did not comprise LH, FSH, and testosterone/LH data for men older than 70 years and in these variables patients' data were compared with data for 70-year-old men from the reference population.

Binary correlations were tested using the Spearman test. Age adjustments were performed using linear regression analyses. In the linear regression analyses variables were included if $P < 0.1$ in binary correlations and variables were log-transformed if the residuals were not normally distributed.

Data are presented as the median (range), mean (standard deviation—SD), t , coefficients (95% confidence interval—CI), counts, or percentages. All tests were two-tailed and the level of significance was taken as $P \leq 0.05$.

3. Results

Twenty patients were initially included in the study and 12 (haemodialysis, $n = 11$; peritoneal dialysis, $n = 1$) completed the intervention (see Figure 1). Dropout during the control period ($n = 5$) and during the training period ($n = 3$) was due to medical complications not related to the study. The patients who dropped out did not differ with regard to age, pretested comorbidity level, body mass index, or hormone profile compared to those who completed the study. The patients' characteristics are presented in Tables 1 and 2.

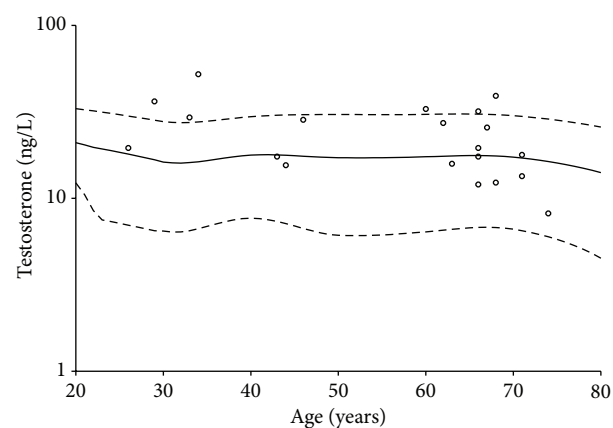
Hormone profiles at baseline for the included patients are presented in Table 2 together with all the available data from the age-matched reference males. The patients' total testosterone was similar to the male reference and correlated negatively with age ($r = -0.456$, $P = 0.04$) (Figure 2). Free testosterone was elevated in the patients compared to the reference (Table 2). For all patients the LH values exceeded the age-matched means for the references (Figure 3), and within the patient group the correlation between LH and age was $r = 0.555$, $P = 0.011$. IGF-1 and IGF-BP3 were significantly higher in the patients compared to the reference group (Table 2), whereas IGF-1/IGF-BP3 did not differ. In correlations between the patients' testosterone and IGF-1, free testosterone was found to be positively associated with IGF-1 ($r = 0.644$, $P = 0.002$).

All hormones were found to be unchanged between baseline and the end of the training period. However, a significant change in total testosterone/LH was found when the delta values of the control period and the training period

TABLE 1: Characteristics of the participants.

Characteristic	($n = 20$)
Age (years)	65 (26–74)
Dialysis modality (HD/PD)	19/1
Duration of chronic dialysis (years)	3.4 (1.1–15.0)
Comorbidities (score 0–3)	3 (1–3)
Body mass index (kg/m^2)	25.6 (18.1–33.5)
Haemoglobin (mmol/L)	7.4 (6.4–9.9)
Albumin (g/L)	42.1 (37.4–49.8)
C-reactive protein (mg/L)	4.0 (0.6–23.0)
Phosphate (mmol/L)	1.8 (0.9–2.4)
Bicarbonate (mmol/L)	25 (17–33)
Primary renal disease	
Type 2 diabetes	1
Hypertension	3
Polycystic kidneys	4
Glomerulonephritis	7
Nephrosclerosis	1
Other/unknown	4

HD: haemodialysis; PD: peritoneal dialysis. Data are presented as median (range) or count.

FIGURE 2: Testosterone levels plotted against the age of the patients. The dots represent male patients undergoing dialysis. Curves are mean \pm 2SD for a male reference population.

were compared (\sim 15% versus +17%, resp.) as presented in Table 3. Body mass index, haemoglobin, albumin, C-reactive protein, phosphate, and bicarbonate remained unchanged throughout the study.

Muscle fibre sizes remained unchanged during the study whereas muscle strength increased significantly by 19–25% during the training period (Table 4).

TABLE 2: Hormone levels for the patients ($n = 20$) and for the age-matched male reference population.

Variables	All patients ($n = 20$)	Reference population	P
Total T (nmol/L)	19.5 (8.2–52.1)	17.6 (16.1–18.0)	0.174
Free T (pmol/L)	473 (174–1057)	289 (226–377)	0.004
IGF-1 (ng/mL)	203 (59–590)	151 (128–276)	0.014
IGF-BP3 (ng/mL)	5045 (3370–9370)	3244 (3020–3983)	<0.001
IGF-1/IGF-BP3	0.0443 (0.0158–0.0630)	0.04652 (0.0400–0.0694)	0.102
SHBG (nmol/L)	42.0 (8.0–132.0)	48.0 (32.9–59.4)	0.211
LH (U/L)	13.0 (5.5–82.8)	4.3 (3.3–4.6)	<0.001
FSH (U/L)	9.7 (1.7–86.1)	7.0 (3.3–7.5)	0.091
Total T/LH	2.1 (0.2–5.0)	4.1 (3.6–5.5)	<0.001
Estradiol (pmol/L)	105 (75–133)	117 (94–123)	0.096
Inhibin-B (pg/mL)	170 (1–403)	142 (134–165)	0.659
Inhibin-B/FSH	18.7 (0.1–235.7)	20.3 (17.9–49.0)	0.445

Data are presented as median (range). T: testosterone; SHBG: sex hormone-binding globulin.

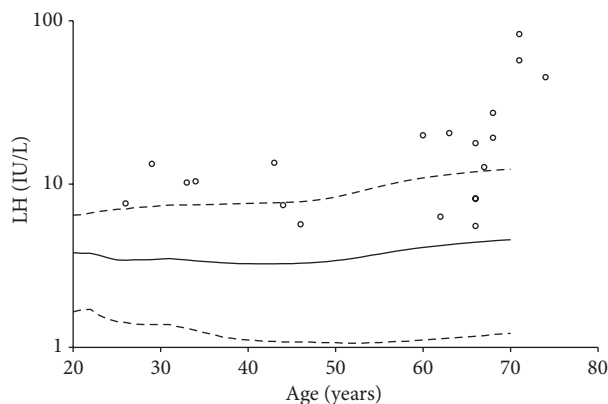


FIGURE 3: Luteinizing hormone levels plotted against the age of the patients. The dots represent male patients undergoing dialysis. Curves are mean \pm 2SD for a male reference population.

3.1. Testosterone and IGF-1 Correlated with Muscle Fibre Size.

In unadjusted binary correlations between baseline tested anabolic hormones and muscle fibre size, free testosterone was found to be positively associated with type 2 muscle fibre size ($r = 0.525$, $P = 0.025$), whereas age-adjusted free testosterone was neither significantly associated with type 1 nor significantly associated with type 2 muscle fibre size (Table 5). Total testosterone was not associated with any muscle fibre size. Unadjusted IGF-1 was positively associated with type 1 fibre size ($r = 0.626$, $P = 0.005$) and type 2 fibre size ($r = 0.598$, $P = 0.009$). When IGF-1 was age-adjusted it remained associated with type 1 fibre size ($P = 0.005$) and type 2 fibre size ($P = 0.012$) (Table 5).

Prior to the training, hormone levels including total testosterone, free testosterone, testosterone/LH, and LH were not associated with individual changes in muscle fibre size during the training period (data not shown).

4. Discussion

To the best of our knowledge, this is the first study to investigate testosterone levels during a resistance training

program in dialysis patients. The patients' serum testosterone levels were not different from those of a reference population whereas LH levels were markedly elevated, indicating a compensated primary Leydig cell insufficiency, a finding that has not been reported in recent studies but was reported in studies published in the 1970s [7]. Even though the testosterone values were within the normal range, the resistance training was not associated with muscle hypertrophy.

Our finding of normal total testosterone levels in the patient group is in contrast to the results of other studies that have detected relatively lower levels of testosterone in dialysis patients [4, 5, 8, 9]. Our study does not provide an explanation for this discrepancy, but we speculate that the results in our patient group may be indicative of a selected healthier subgroup of patients than previously published work. This speculative interpretation may, however, be supported by the patients' motivation to participate in a comprehensive training program. An increased LH level as a response to decreased Leydig cell capacity is an example of the classical endocrine feedback loop where the endocrine system tends to keep the peripheral hormones at a steady level. In our dialysis patients the decreased Leydig cell capacity was compensated by an increased LH stimulation. However, in general, some men go from being eugonadal (i.e., having normal testosterone levels on a background or normal LH levels) to having a compensated hypogonadism as our patients. Some patients may further develop an overt primary hypogonadism where an increased LH level is insufficient to compensate for the decreasing Leydig cell capacity as suggested by the European Male Aging Study [18]. The findings of reduced testosterone levels in previous studies of dialysis patients may reflect that these in general have reached the stage of primary hypogonadism. It is most likely the impaired kidney function in the dialysis patients that causes the decreasing Leydig cell capacity. To our knowledge it remains to be established to which degree testosterone deficient dialysis patients will benefit from a testosterone substitution therapy. However, it is tempting to speculate that they will benefit as many of the classical symptoms [18] between these two diseases overlap. Thus, our findings

TABLE 3: Hormone levels for those patients who completed the intervention ($n = 12$). The 16-week control period was measured from the baseline test to the pretraining test, and the 16-week training period was measured from the pretraining to the posttraining test.

Variables	Baseline ($n = 12$)	Pretraining ($n = 12$)	Posttraining ($n = 12$)	P control period	P training period	P between periods
Total T (nmol/L)	21.7 (8.2–52.1)	18.7 (7.8–54.7)	19.8 (7.2–57.7)	0.695	0.326	0.099
Free T (pmol/L)	485 (141–1057)	474 (177–820)	524 (240–776)	0.695	0.530	0.347
IGF-1 (ng/mL)	203 (138–590)	246 (108–811)	201 (113–606)	0.346	0.272	0.388
IGF-BP3 (ng/mL)	4905 (3600–9370)	4740 (3610–9760)	4525 (3550–8900)	0.754	0.844	0.937
IGF-1/IGF-BP3	0.0443 (0.0313–0.0630)	0.0461 (0.0262–0.0831)	0.0423 (0.0267–0.0895)	0.433	0.182	0.347
SHBG (nmol/L)	42.5 (13.0–66.0)	35.0 (11.0–80.0)	38.5 (8.0–83.0)	0.235	0.366	0.239
LH (U/L)	13.4 (5.5–57.2)	15.8 (5.6–58.7)	14.4 (5.5–52.0)	1.000	0.424	0.477
FSH (U/L)	10.5 (4.1–86.1)	9.7 (3.9–84.0)	8.9 (3.3–83.7)	1.000	0.272	1.000
Total T/LH	1.83 (0.18–5.01)	1.55 (0.24–2.86)	1.82 (0.34–3.70)	0.084	0.110	0.041
Estradiol (pmol/L)	101 (75–133)	104 (70–113)	101 (68–125)	0.432	0.694	0.638
Inhibin-B (pg/mL)	170 (1–342)	162 (1–380)	172 (1–355)	0.929	0.721	0.575
Inhibin-B/FSH	15.35 (0.01–83.82)	15.77 (0.01–88.99)	20.31 (0.01–107.90)	0.937	0.136	0.209

Data are presented as median (range). T: testosterone; SHBG: sex hormone-binding globulin; DHEA: dehydroepiandrosterone; AMH: anti-Müllerian hormone.

TABLE 4: Muscle fibre size and muscle strength for those patients who completed the intervention ($n = 12$). The control period was between the baseline and pretraining test. The training period was between the pretraining and the posttraining test.

Variables	Baseline	Pretraining	Posttraining
Muscle fibre size			
Type 1 (μm^2)	4896 (3138–8453)	4760 (2853–7891)	4730 (2273–9204)
Type 2 (μm^2)	3485 (2778–6067)	3246 (2284–5336)	3832 (2829–6953)
Knee extension strength			
Right (N)	349 (195–511)	349 (200–583)	460 (258–695)***
Left (N)	299 (216–595)	341 (193–558)	400 (238–657)**

Data are presented as median (range). N: Newton. Between pretraining and posttraining ** $P < 0.010$; *** $P < 0.005$.

encourage a more detailed investigation focussing on this aspect.

Testosterone was unchanged after training and this was not surprising since the baseline values were relatively high. Testosterone/LH was also found to be unchanged after training. However, the statistical analyses showed a significant difference between delta values when comparing the control period with the training period. A slight decrease over the control period was followed by a slight increase over the training period in terms of the testosterone/LH value, resulting in a 32% net increase. This finding is most likely a chance finding, being the result of normal variation in testosterone. On the other hand, it cannot be excluded that a decrease in testosterone/LH in the patient sample was counteracted by a reverse through training. If this is indeed a true effect of training, then the underlying mechanism is not obvious. If the decrease in testosterone/LH was a true finding, it could be the result of improved metabolism leading to an improved testes function. However, further studies are needed before we are able to draw more definitive conclusions about such a relation.

The training intervention was not associated with muscle hypertrophy at the fibre level, which was an unexpected result. One would expect hypertrophy after a period of high load resistance training [19] especially when testosterone

values are within a normal range. Indeed, the effect of resistance training on muscle mass is in general associated with testosterone level [20]. In healthy young men who conducted resistance training, an increase in muscle mass was significantly greater in subjects with normal testosterone compared to subjects with a suppressed testosterone level [20]. The anabolic effect of the training in our study may have been counteracted by impaired muscle protein synthesis or increased protein breakdown due to comorbidities [21, 22], as well as regular dialysis treatment [23]. Thus the significant effect on muscle strength observed in these patients may be primarily the result of neuromuscular improvements [24]. However, our study may have a relatively low statistical power, and one cannot ignore the possibility that the unchanged muscle fibre size that was observed could be the result of a type II error.

The relatively high levels of circulating IGF-1 and IGF-BP3 are in line with another study of resistance training in dialysis patients [25], although a decrease in IGF-1 following resistance training has also been reported [26]. Our finding of a positive association between IGF-1 and muscle fibre size at baseline is supported by MacDonald and colleagues who found a positive correlation between lean body mass and circulating IGF-1 in dialysis patients [27]. Whether circulating IGF-1 has a more significant role in muscle anabolism

TABLE 5: Age adjusted free testosterone and IGF-1 correlations with muscle fibre size (dependent variables).

Muscle fibre size	Free testosterone (pmol/L)			IGF-1 (ng/mL)		
	<i>t</i>	Coefficient* (95% CI)	<i>P</i>	<i>t</i>	Coefficient* (95% CI)	<i>P</i>
Type 1 (μm^2)	1.61	0.00 (0.00-0.00)	0.128	3.29	0.35 (0.12–0.58)	0.005
Type 2 (μm^2)	1.83	1.596 (–0.259–3.450)	0.087	2.84	2348 (586–4110)	0.012

* Unadjusted. CI: confidence interval.

in patients undergoing dialysis compared to healthy subjects remains unknown.

The present study has important limitations. The sample size was small and heterogeneous in terms of age and dialysis duration. Furthermore, we did not measure body composition using scanning methods, which would have been interesting in addition to the data for muscle size at the fibre level. Finally, the study was limited by the nonrandomised design as a time series design was used. The design was used to elevate the number of patients, who received the intervention. However, a considerable strength of this study is that it presents data from a rigorous relatively long period of resistance training.

In conclusion, well treated male patients undergoing dialysis may counteract impaired Leydig cell function through elevated LH secretion. Even though testosterone and IGF-1 values were in or above the normal range for healthy individuals, the patients did not achieve muscle hypertrophy after a rigorous period of high load resistance training.

Conflict of Interests

The authors report no conflict of interests.

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Clinical Study

Resistance Exercise with Older Fallers: Its Impact on Intermuscular Adipose Tissue

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Objective. Greater skeletal muscle fat infiltration occurs with age and contributes to numerous negative health outcomes. The primary purpose was to determine whether intermuscular adipose tissue (IMAT) can be influenced by an exercise intervention and if a greater reduction in IMAT occurs with eccentric versus traditional resistance training. **Methods.** Seventy-seven older adults (age 75.5 ± 6.8) with multiple comorbidities and a history of falling completed a three-month exercise intervention paired with either eccentric or traditional resistance training. MRI of the mid-thigh was examined at three time points to determine changes in muscle composition after intervention. **Results.** No differences in IMAT were observed over time, and there were no differences in IMAT response between intervention groups. Participants in the traditional group lost a significant amount of lean tissue ($P = 0.007$) in the nine months after intervention, while participants in the eccentric group did not ($P = 0.32$). When IMAT levels were partitioned into high and low IMAT groups, there were differential IMAT responses to intervention with the high group lowering thigh IMAT. **Conclusions.** There is no decrease in thigh IMAT after a three-month exercise intervention in older adults at risk for falling and no benefit to eccentric training over traditional resistance training for reducing IMAT in these individuals.

1. Introduction

Aging is associated with increased fatty infiltration of skeletal muscle [1–5]. These age-associated changes in muscle composition, specifically elevated levels of intermuscular adipose tissue (IMAT), have been linked to a number of negative health consequences and functional impairments [5], including increased risk of hospitalization [6], mobility impairments [7, 8], strength deficits [1, 5], poor aerobic capacity [9], and poor performance on common clinical assessments, such as the 6-Minute Walk Test [10] and Five Times Sit-to-Stand Test [11]. Additionally, elevated levels of IMAT in older adults are positively associated with insulin resistance [12–14], perhaps due to the essential role of skeletal muscle in glucose disposal [13]. Because IMAT typically increases with age and may contribute to other morbidities that occur with advancing age, it is a priority to explore approaches by which IMAT levels may be reduced to diminish the personal and societal costs of age-associated skeletal muscle fat infiltration [5].

An inverse relationship exists between habitual physical activity of older adults and skeletal muscle fat infiltration [15–17], though the concept that older adults' level of IMAT is amenable to change with a focused rehabilitation program is less clear. The link between habitual physical activity levels and IMAT has been demonstrated in masters athletes [15], in diabetic older adults [16], and in older adults with peripheral arterial disease [17]. Only few studies, however, have demonstrated the effects of exercise interventions on IMAT. In one of these studies, Goodpaster et al. [18] demonstrated that a 12-month, multimodal exercise program prevented the age-associated increase in IMAT observed in an inactive control group during the intervention period. Decreases in IMAT have been reported in cohorts of healthy, community-dwelling older men and women after completing six months of multimodal exercise [19, 20]. Further, reductions in IMAT in community-dwelling older adults can occur with or without concomitant weight loss interventions coupled to multimodal physical activity programs [19]. Finally, strength training over 3–6 months has resulted in decreased levels

of IMAT in elderly men and women [21, 22] and older adults with a variety of comorbid conditions [2]. However, the optimal type and intensity of resistance exercise as part of a multimodal rehabilitation program for reducing or preventing IMAT infiltration in an older, at-risk population is unknown. Additionally, since some have reported a differential muscle function response to exercise in those with high versus low initial levels of IMAT [23], it is curious if a differential gross muscle structure (change in IMAT) response occurs upon completion of a multimodal exercise program.

Several studies [18–20] have examined the effects of resistance training on IMAT as part of a multimodal exercise program in older adults, though only one has reported on the exclusive use of eccentric resistance training [2]. This heterogeneous cohort included survivors of stroke or cancer, individuals with impaired glucose tolerance or multiple sclerosis, and subjects who had undergone a total knee replacement, thereby making it difficult to generalize the IMAT results to a population of older adults participating in a focused rehabilitation intervention. Compared with traditional resistance exercise, which combines concentric and eccentric muscle contractions, resistance training exclusively using eccentric muscle contractions can result in higher levels of force production, making it a potentially higher intensity mode of resistance exercise [24]. This higher intensity eccentric training can also be performed at lower energetic costs and perceived exertion levels [24–26]. Several recent review papers [27–29] have characterized eccentric exercise as high intensity and documented its positive effect on muscle and rehabilitation outcomes. It is unknown, however, what effect eccentric training may have on IMAT as compared to traditional resistance exercise as part of a multimodal exercise program for older adults.

Therefore, the primary purpose of this study was to examine the effects on IMAT of eccentric resistance training, as compared to traditional resistance training, as part of a multicomponent exercise fall reduction program in older adults at risk for falls. The secondary purpose was to describe if the participants responded differently to resistance exercise in terms of changes in muscle composition when partitioned into high and low IMAT groups.

2. Methods

2.1. Participants and Time Points. Seventy-seven older adults (75.5 ± 6.8 years, 20 males, and 57 females), who experienced an unintentional fall to the ground in the past year, volunteered to participate in this randomized multicomponent exercise fall reduction study that included either a traditional (TRAD) or eccentric (ECC) resistance training program. The participants were assessed on three occasions, at pretraining, posttraining, and at a nine-month follow-up time point. A block randomization process was used for assigning participants into either the ECC or TRAD groups (see CONSORT flow diagram, Figure 1). Participants were required to be ambulatory within the community with or without an assistive device yet they have two or

more comorbid conditions. Written informed consent was obtained and the Institutional Review Board at the University of Utah approved the study procedures. Individuals with progressive neurological disorders, active cancer, chronic heart failure, or unstable medical conditions that precluded exercise were excluded. Baseline assessments included self-report of comorbidities and clinical measurements of gait speed and BMI.

2.2. Intervention. Participants trained for 60 minutes per session, three times per week for 12 weeks as part of a multicomponent exercise fall reduction program that included resistance training of the lower extremity. Training sessions consisted of multiple modes of exercises performed in a circuit that alternated higher intensity and dynamic activities with lower intensity, static tasks. Aerobic exercise was performed on a NuStep recumbent trainer (NuStep Inc, Ann Arbor, MI), seated stationary cycle ergometer, or overground treadmill. Flexibility exercises included pectoralis stretching in a doorway, seated hamstrings stretching, standing calf stretching, hooklying trunk rotations, and prone-on-elbows as tolerated. Balance exercises were performed with both static and dynamic bases of support and incorporated varied vestibular and visual inputs for altered sensory stimulation. Upper extremity resistance exercise was performed using free weights. The only difference in the multicomponent exercise fall reduction program was the type of lower extremity resistance training performed. There was no attempt at matching the workloads of the two resistance exercise (TRAD versus ECC) regimens, though the amount of time spent doing resistance exercise progressed in both groups to a maximum of 15 minutes. The TRAD group performed three sets of 15 repetitions of a seated bilateral leg press exercise (Tuff Stuff PS-230 Deluxe Leg Press, Tuffstuff, Chino, CA) at 60–65% of their one repetition maximum (RM) for the initial two weeks. Training sessions for the remaining 10 weeks were performed at 70% of 1-RM, which was assessed every two weeks thereafter. In addition, the TRAD group performed standing multidirectional straight leg exercises with a weighted cuff placed just proximal to the ankle. The training loads for this exercise were increased as tolerated every two weeks provided the participants could complete three sets of 15 repetitions. The ECC group performed a progressive resistive eccentric exercise of the knee and hip extensor muscles using a recumbent stepper-ergometer (Eccentron, Baltimore Therapeutic Equipment, Hanover, MD) as described previously [26, 29, 30]. Briefly, the stepper speed ranged between 12 and 18 revolutions per minute as the participant resisted the stepper pedal action and eccentric muscle contractions were induced in the knee and hip extensor muscles. Visual feedback of the work performed for each revolution was displayed on a computer monitor. Participants performed eccentric work from approximately 15–75 degrees of knee flexion as they resisted the motorized movement of the stepper pedals via resistance action of the knee and hip extensors. Perceived exertion was assessed with the Borg rating scale between 6 and 20 [31]. In the first week of ECC, sessions lasted three to five minutes and were performed at a “very, very light”

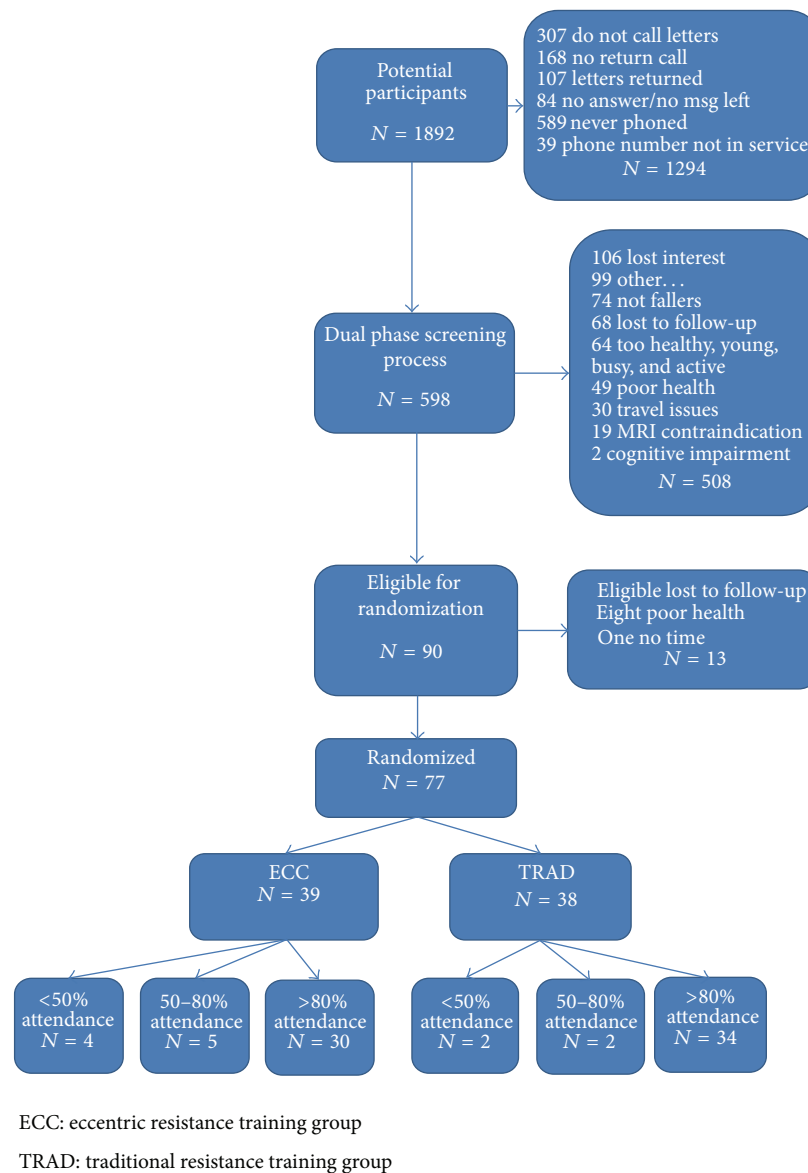


FIGURE 1: CONSORT flow diagram.

intensity while resisting the stepper pedal action. During subsequent weekly training sessions, subjects were gradually allowed to resist the pedal action with more exertion as they progressed from a “fairly light” to a “somewhat hard” intensity level. The duration of each session was progressively increased to maximal 15 minute duration of ECC.

2.3. IMAT Determination. Magnetic resonance imaging (MRI) was used for determination of the cross-sectional area (CSA) of lean muscle mass and IMAT as has been done previously [7]. The primary outcome variable in this study was IMAT CSA. Bilateral MRI scans of the thighs were obtained and subjects were placed supine in a 3.0 Tesla whole body MR imager (Siemens Trio, Siemens Medical, Erlangen, Germany). The legs were scanned in a coronal plane and the

midpoint of the thigh was determined and defined as half way between the superior margin of the femoral head and the inferior margin of the femoral condyles. Axial imaging (5 mm thick slices at 1 cm intervals) of the legs was then performed over half the length of the femur, centered at the midpoint of the thigh. Separate fat and water images were created with custom software using the three-point Dixon method [32]. A tissue model was then used to calculate estimates of total fat and nonfat volume fractions on a per-pixel basis, which were displayed in image form. A single image slice from the midpoint of each thigh was used to determine average cross-sectional area (cm²) of IMAT and lean tissue. Manual tracing eliminated subcutaneous fat and bone and isolated the fascial border of the thigh to create a subfascial region of interest (ROI). Total IMAT and lean tissues were calculated by summing the value of percent fat fraction and

percent lean tissue fraction over all pixels within the ROI using custom-written image analysis software (MATLAB; The MathWorks, Natick, MA). This sum was multiplied by the area of each pixel to give total fat and lean tissue CSAs within the ROI and the respective IMAT and lean tissue cross-sectional areas were calculated after excluding subcutaneous adipose tissue and bone [32]. The same investigator blinded to group performed measurements of individual participants. This technique has demonstrated high levels of intrarater reliability [30], test-retest reliability [33], and concurrent validity when compared to imaging of a cadaveric phantom limb [30]. To normalize IMAT for thigh size, the percent of IMAT was calculated for each individual. This was done by dividing the area of IMAT (in cm^2) by the overall area of the thigh (in cm^2) excluding subcutaneous adipose tissue and bone. In the partitioning of the participants into a high or low IMAT category, participants from both intervention groups were stratified into high and low IMAT groups by percent fat (IMAT area/total muscle area) above or below the collective mean.

2.4. Statistical Analysis. To address the primary purpose of the study and to determine whether resistance training with ECC or TRAD induced thigh muscle composition (IMAT and lean changes), a two-way repeated measures analyses of variance (ANOVA) with the factors of group (ECC or TRAD) and time (pretraining, posttraining, and nine-month follow-up) was utilized at an alpha level of 0.05. The main effects and interaction effects were analyzed and pair-wise post hoc comparisons were employed when significant findings occurred. Separate one-way repeated measures analyses of variance were employed to determine within-group changes over time. Finally, to address the secondary purpose and determine whether there was a differential response to resistance exercise as an intervention by those with high or low IMAT content, a separate one-way repeated measures analysis of variance for the high and low IMAT groups, respectively, was used to assess changes in each group across each of three time points. The data was analyzed using SPSS version 20 (SPSS Inc, Chicago, IL).

3. Results

The ECC and TRAD intervention groups were not statistically different at baseline (see Table 1). There were no significant time ($P = 0.89$), group ($P = 0.21$), or interaction effects ($P = 0.63$) for changes in IMAT. A significant time effect for changes in lean ($P = 0.007$) occurred, though there were no significant group ($P = 0.31$) or group by time interaction ($P = 0.21$) effects for changes in lean. Within-group changes in each intervention group are shown in Table 2. There were no significant within-group changes in IMAT over time in either the ECC ($P = 0.92$) or TRAD ($P = 0.64$) groups. However, there was a significant ($P = 0.007$) within-group change in lean for the TRAD group, with the lean cross-sectional area at the nine-month follow-up being significantly lower than either the pretraining ($P = 0.02$) or posttraining ($P = 0.05$) values. There were no significant

TABLE 1: Participant characteristics.

	Eccentric ($n = 39$)	Traditional ($n = 38$)	P
Gender (F : M)	29 : 10	27 : 11	0.74
Age (years)	76.2 (7.4)	74.6 (6.2)	0.32
BMI (kg/m^2)	27.1 (4.8)	29.1 (6.2)	0.11
Gait speed (m/s)	1.14 (0.24)	1.10 (0.25)	0.42
Comorbidities	5.2 (2.2)	5.3 (2.0)	0.82

Mean (\pm SD); BMI: Body Mass Index; comorbidities: number of self-reported comorbid conditions at baseline.

within-group changes in lean over time in the ECC group ($P = 0.32$). Neither the ECC ($P = 0.51$) nor the TRAD ($P = 0.15$) group demonstrated a significant change in BMI over time.

When stratifying the participants from both intervention groups by the relative amount of IMAT in their thighs (see Table 3), the high IMAT (14.5% or more) group demonstrated a loss of lean tissue CSA nine months after training ($P = 0.04$), while the low IMAT (14.4% or less) group did not change their lean tissue CSA ($P = 0.18$). Both the high and low IMAT groups, however, demonstrated changes in IMAT with the former losing ($P = 0.014$) and the latter gaining ($P = 0.005$) IMAT during the intervention. Further, the high IMAT group experienced a parallel lowering ($P = 0.03$) of their elevated pretraining BMI, while the low IMAT group's BMI did not change ($P = 0.73$). There was no difference in the number of self-reported comorbidities between the high and low IMAT groups at baseline ($P = 0.39$), although the high IMAT group did show a greater proportion of self-reported diabetes mellitus ($P = 0.01$) and hypertension ($P = 0.008$).

4. Discussion

The primary findings of this study indicate that a three-month, multimodal, fall prevention program for at-risk, community-dwelling, older adults did not induce a change in thigh IMAT when the program was paired with either eccentric or traditional resistance training. Further, thigh lean tissue area did not change during the intervention period, though a significant decline in lean mass was seen in the nine months following the conclusion of the exercise intervention. This decline in lean mass after the intervention period was greater in the traditional group than in the eccentric resistance training group.

Previous studies have examined the effects of multimodal exercise training on skeletal muscle composition in older adults and have shown that IMAT may have the capacity to change with specific exercise intervention protocols [19, 20, 22]. Other studies have shown favorable changes in IMAT with resistance training alone [2, 21]. However, some longitudinal studies have refuted this concept, citing no change in skeletal muscle fat infiltration with exercise [18, 34]. In one such study, Goodpaster et al. [18] suggested that a 12-month, multimodal, exercise intervention in a cohort of older adults prevented the increase in IMAT seen in their inactive control group over the same 12-month period. In the absence of a formal exercise intervention, a significant annualized

TABLE 2: Muscle composition outcomes for eccentric and traditional resistance training groups.

	Eccentric group (<i>n</i> = 39)				Traditional group (<i>n</i> = 38)			
	Pretraining	Posttraining	Nine-month follow-up	Within-group change	Pretraining	Posttraining	Nine-month follow-up	Within-group change
IMAT (cm ²)	29.53 (8.3)	29.56 (7.8)	29.33 (8.8)	<i>P</i> = 0.92	32.11 (11.4)	31.75 (10.2)	32.41 (9.3)	<i>P</i> = 0.64
Lean (cm ²)	181.8 (34.2)	183.9 (34.1)	181.6 (31.2)	<i>P</i> = 0.32	193.1 (48.7)	193.9 (48.2)	188.6 (46.8)	<i>P</i> = 0.007

Eccentric group: participants who participated in eccentric resistance training as part of multimodal exercise program; traditional group: participants who participated in traditional resistance training as part of multimodal exercise program; lean: lean tissue cross-sectional area of mid-thigh; IMAT: intermuscular adipose tissue cross-sectional area of mid-thigh.

TABLE 3: Muscle composition outcomes for participants with high and low muscle fat fractions.

	High IMAT (<i>n</i> = 35)				Low IMAT (<i>n</i> = 42)			
	Pretraining	Posttraining	Nine-month follow-up	Within-group change	Pretraining	Posttraining	Nine-month follow-up	Within-group change
IMAT (cm ²)	37.75 (8.8)	35.56 (8.8)	36.20 (8.6)	<i>P</i> = 0.014	25.01 (6.7)	26.53 (7.0)	26.38 (6.9)	<i>P</i> = 0.005
Lean (cm ²)	181.6 (36.6)	183.2 (35.6)	178.6 (32.4)	<i>P</i> = 0.04	192.1 (46.1)	193.5 (46.1)	190.4 (44.4)	<i>P</i> = 0.18
% IMAT	17.24 (2.2)	16.27 (2.5)	16.88 (2.6)	<i>P</i> = 0.002	11.54 (1.6)	12.15 (2.4)	12.26 (2.2)	<i>P</i> = 0.012
BMI (kg/m ²)	30.02 (5.3)	29.87 (5.1)	29.46 (5.2)	<i>P</i> = 0.03	26.42 (5.4)	26.42 (4.9)	26.24 (4.9)	<i>P</i> = 0.73

Mean (±SD); high IMAT >14.5% IMAT, low IMAT <14.5% IMAT; IMAT: intermuscular adipose tissue cross-sectional area; lean: lean tissue cross-sectional area; %IMAT: fraction IMAT per total lean and IMAT area of the mid-thigh; BMI: Body Mass Index.

increase in skeletal muscle fat infiltration was also reported in a sample of 1678 older adults from the Health ABC study cohort [3]. Therefore, the lack of change in IMAT over a one-year period in the present study may be a positive finding, although it is impossible to draw such a conclusion without a randomized, inactive control group for comparison.

A novel observation in the present study is that there may be a differential IMAT response to multimodal exercise interventions in older individuals at risk for falling. That is, participants characterized as high IMAT and a higher BMI responded differently than those whose initial levels of IMAT were low. This differential response to resistance exercise has been demonstrated in muscle function, that is, muscle quality [23], but not in muscle composition. When partitioned by the fraction of IMAT making up the mid-thigh cross-sectional area, participants with high IMAT content, defined as percent of mid-thigh IMAT above the mean, demonstrated a significant decline in both BMI and IMAT after multimodal exercise. It is possible that the decrease in IMAT observed in the high IMAT group is a reflection of that group's decrease in BMI. However, post hoc analysis of these changes shows that the significant change in IMAT occurred from pre- to posttraining (3-month duration), while the significant change in BMI for this group occurred from pretraining to the final follow-up (12-month duration). It is curious, therefore, that the changes in IMAT in the high IMAT group are not directly parallel to the changes in BMI. These observations suggest that the benefits of exercise for skeletal muscle composition may be greater for older adults with poorer muscle composition upon initiation of a multimodal exercise program. These benefits, however, apply only for the duration of a structured exercise intervention, since the older individuals considered to have high IMAT lost

a significant amount of lean mass during the 9-month follow-up, while the low IMAT group did not.

This differential response of those with higher IMAT levels to the multimodal exercise intervention is a possible explanation for the lack of significant changes in IMAT seen in the two respective intervention groups. Other possible explanations include greater proportions of reported diabetes mellitus and hypertension in the high IMAT participants, the relatively short duration (three months) of the intervention compared to other studies (18-week to 12-month duration) [18–22] that favorably impacted IMAT levels, and the quantification of IMAT by MRI, which differentiates tissue types by signal characteristics [5, 35] rather than CT, which indirectly measures IMAT content by muscle attenuation [5, 36]. Additionally, our participants were at-risk fallers with an average of five comorbid conditions, which makes them fundamentally different from the healthy, moderately-functioning older adults included in similar studies [18, 21, 22]. These clinically distinct differences in the health of participants make these findings novel and may account for some of the discrepancies between our results and the results of previously published studies.

This study has several limitations. All subjects reported multiple comorbidities at baseline and a history of falls, so the results cannot be generalized to a population of nondisabled elderly. Further, the sample size was relatively small when separating the groups, and there was no inactive control group for comparison of results. Despite these limitations, there are clear conclusions drawn and some interesting questions raised.

An unexpected finding from this study was that participants with low initial IMAT demonstrated a significant increase in IMAT during the intervention period without

concomitant change in BMI. Though one might expect individuals with low IMAT to have a more ideal muscle composition, the trend for both the high and low IMAT groups to converge toward an intermediate IMAT fraction with an exercise intervention introduces the question of whether there is an optimal level of IMAT that is desirable for aging skeletal muscle. Future studies should further examine this differential response of IMAT to exercise interventions, as well as other exercise interventions that may reduce the rate of fatty infiltration of skeletal muscle.

5. Conclusions

There is no decrease in thigh IMAT following a three-month, multicomponent exercise, fall reduction program in high fall-risk, older individuals and no differential impact of eccentric resistance training over traditional resistance training for muscle composition. The observed differential effects of training on those with higher amounts of IMAT at baseline provide an alluring direction for future study and should be confirmed.

Conflict of Interests

One of the authors Paul LaStayo is a coinventor on the ergometer licensed to Eccentron, BTE Technologies Inc., Hanover, MD, USA. Neither Paul LaStayo nor any of the other authors have received any financial incentives (e.g., reimbursements, fees, royalties, funding, or salary) from the company or stemming from the contents of this paper or any related published papers.

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Clinical Study

Interleukin-6 and Vitamin D Status during High-Intensity Resistance Training in Patients with Chronic Kidney Disease

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Background. The aim of this study was to investigate IL-6 and 25-hydroxyvitamin D (25-OH D) associations with muscle size and muscle function in dialysis patients. **Methods.** Patients were included in a 16-week control period followed by 16 weeks of high-intensity resistance training thrice weekly. IL-6 and 25-OH D were analysed after an over-night fast. Muscle fibre size was analysed in biopsies from *m. vastus lateralis*. Muscle power was tested using a Leg Extensor Power Rig. **Results.** Patients ($n = 36$) with IL-6 ≥ 6.49 pg/ml (median) were older and had decreased muscle power and a reduced protein intake ($P < 0.05$) compared with patients with IL-6 < 6.49 pg/ml. IL-6 was not associated with muscle fibre size. Vitamin D deficiency (25-OH D < 50 nmol/l) was present in 51% of the patients and not associated with muscle power. IL-6 remained unchanged during the training period, whilst muscle power increased by 20–23% ($P < 0.001$). **Conclusion.** Elevated IL-6 values were associated with decreased muscle power but not with decreased muscle fibre size. Half of the patients were suffering from vitamin D deficiency, which was not associated with muscle power. IL-6 was unchanged by high-intensity resistance training in dialysis patients in this study.

1. Introduction

Chronic kidney disease (CKD) can arise as the result of several diseases, among them diabetes. When renal function is reduced to approximately 10% of the healthy renal capacity of an individual, dialysis therapy or kidney transplantation is needed in order to keep the patient alive. The majority of patients with CKD are treated with haemodialysis thrice weekly or daily by means of peritoneal dialysis.

Low-grade systemic inflammation with increased levels of proinflammatory cytokines is common in patients with CKD [1]. The origin of this low-grade inflammation in patients with CKD is not clear, but it could be a complication related to either impaired kidney function or dialysis

treatment *per se*, or both [2]. The low-grade inflammation is likely to contribute to the high mortality rate in dialysis patients via an elevated protein energy waste [3, 4]. Whilst protein energy waste increases the mortality risk, it may also affect muscle mass negatively and thereby reduce the patients' muscle strength. Thus, a direct link between low-grade inflammation and a decrease in muscle strength impairing physical performance and reduced ability to perform daily activities is likely.

In subjects not suffering from CKD, low-grade inflammation is associated with physical inactivity [5]. As physical inactivity is a common problem in dialysis patients, the question remains as to whether low-grade inflammation in these patients can be reduced by physical exercise. Previous

TABLE 1: Protocol of 48 exercise sessions covering the 16 weeks of the training.

Exercise	Session 1–6	Session 7–12	Session 13–24	Session 25–36	Session 37–42	Session 43–48
Leg press (sets · reps)	4 · 15	5 · 15	5 · 12	5 · (8–10)	5 · (6–8)	4 · (6–8)
Knee extension (sets · reps)	3 · 15	3 · 15	4 · 12	5 · (8–10)	5 · 8	4 · 8
Knee flexion (sets · reps)	3 · 15	3 · 15	4 · 12	4 · 10	4 · 8	4 · 8

Reps: repetitions.

studies have not shown any effect of exercise training on low-grade inflammation in dialysis patients, but the results may be affected by the training modalities and programs used.

In parallel with low-grade inflammation, vitamin D deficiency determined as low values of 25-hydroxyvitamin D (25-OH D) is common in patients with CKD [6–8]. The vitamin D deficiency in patients with CKD arises from a diminished exposure to sunlight and through malnutrition. Vitamin D deficiency has serious implications in terms of reduced muscle function [9] and an increased mortality risk in dialysis patients [6]. Furthermore, it is likely that an impact of vitamin D deficiency on muscle function may be present in CKD patients even before dialysis therapy is needed [10]. The causality between vitamin D deficiency and reduced muscle size is not clear, but vitamin D deficiency may impair protein synthesis leading to muscle waste [11].

Thus, low-grade inflammation and vitamin D deficiency may have a negative impact on muscle mass and muscle function in dialysis patients. The aim of this study was to investigate the effect of resistance training on the proinflammatory factor IL-6 as well as the impact of 25-OH D on muscle size in dialysis patients.

2. Material and Methods

The data from the present study were obtained as part of a recent study of effects of resistance training in dialysis patients [12]. The patients were recruited from three dialysis centres in the Capital Region, Denmark, to a control period of 16 weeks without any intervention followed by an intervention period of 16 weeks with resistance training. The study was performed with three cohorts over three periods of time. To be included, the participants had to be above 18 years of age and undergoing haemodialysis or peritoneal dialysis for more than three months. Exclusion criteria were insulin treatment, severe diabetic retinopathy, leg amputation, severe peripheral polyneuropathy, dementia, and an inability to speak Danish. The capacity of the study program allowed all included patients to participate.

Comorbidity level was assessed using the Index of Coexistent Disease [13]. Food intake was assessed using a modified 7-day version of the Inter99 food frequency questionnaire [14] and energy intake was determined with the aid of Master Diætist Data software (Anova A/S, Holte, Denmark).

The tests were conducted with the same relation to the dialysis schedule at the three tests. Informed consent was obtained from all patients and the local ethical committee

approved the protocol (H-D-2008-124). The study was registered on controlled-trials.com no. ISRCTN72099857.

2.1. Training Program. The training consisted of supervised progressive high-intensity resistance training three times a week for 16 weeks [12]. The training began with 5 minutes of warm-up followed by up to 5 sets of dynamic leg press, dynamic leg extension, and dynamic leg curl, respectively. The rest period between each set was 60–90 seconds (the time between repetitions was not regulated). During the intervention period the load was increased and the number of repetitions decreased correspondingly from 15 repetitions in the beginning of the intervention period to 6 repetitions in the final period (see Table 1). Every set was performed to exhaustion. The progression during the training period was adjusted according to changes in 1 repetition maximum (RM). The 1RM was tested six times in the exercise machines used in the training program (Technogym, Rotterdam, The Netherlands) prior to the subperiods presented in Table 1 (first test day 1, week 1). After 5 minutes of warm-up, the participants completed a full concentric knee extension from a 90-degree flexion while sitting in an upraised position to test knee extension 1RM. In the 1RM test, the first attempt was conducted close to an estimated maximum strength and the following attempts were conducted with an increased resistance of 2.5 to 10 kg. The muscle strength test was conducted with a maximum of 6 attempts and the highest value was accepted as the result. Rest period between each attempt was 60 seconds. Every participant conducted the test with the same machine position at “pretraining” and at “posttraining” test. The load in the leg press exercise was also determined using the previously described testing protocol. In the leg press test the participants completed a full concentric knee extension from 90-degree flexion in the knee and hip joints. The knee extension and the leg press tests were conducted on the same days in the presented order. The training intensity was calculated using the relations 6RM ~90% of 1RM; 8RM ~86% of 1RM; 10RM ~82% of 1RM; 12RM ~77% of 1RM; and 15RM ~71% of 1RM. Three patients did not feel comfortable during the high loaded 1RM tests, which were replaced by 6RM tests used in the intensity progression. The 1RM tests were conducted on training days before the exercises. The intensity progression during the 16 weeks of training was in addition to the 1RM tests based on increased muscle strength observed between the 1RM tests during the intervention period. Thus, as the patients were able to exceed the estimated number of repetitions according to the training protocol, the load was elevated immediately. In the leg curl

exercise, the intensity was not based on 1RM tests but on the number of repetitions performed to exhaustion during the training program.

Whilst the predefined number of repetitions during every training session was completed in the first two to three sets, the number of repetitions usually declined in the following sets as exhaustion was achieved earlier.

2.2. Muscle Power and Physical Function. Leg extensor power was measured using the Nottingham Leg Extensor Power Rig. The patients sat in an upright position with their arms folded across their chest and with their active leg towards the push-pedal in front of the seat, which made the direction of movement almost horizontal. The subject was instructed to push the pedal as hard and as fast as possible. The measurement was repeated at least five times and until no further improvement could be recorded on two consecutive occasions. The data were recorded, computed, and expressed in watts (W) using the Leg Rig software package (PC214E; University of Nottingham, Medical Faculty Workshops, Queen's Medical Centre, Nottingham, UK).

Physical function was measured using the Chair Stand Test from the Senior Fitness Test [15]. The test required the patients to rise to a full standing position and return to a seated position as frequently as possible within a 30-second time frame whilst maintaining their arms folded across their chest at all times.

2.3. Muscle Fibre Analyses. Muscle biopsies were obtained from the midregion of *m. vastus lateralis* on nonhaemodialysis days through a five-millimetre incision using a Bergström biopsy needle. Serial sections (10 μm) of the muscle biopsy samples were cut and myofibrillar ATPase histochemistry was performed at pH 9.40 after preincubation at pH values 4.37, 4.60, and 10.30 [16]. Computer image analysis was performed using an image analysis system. Fibres were subsequently classified as type 1, type 2A, and type 2X [17]. Fibre type sizes were only performed on the two major fibre types (1 and 2). Only truly horizontally cut fibres were analyzed.

2.4. Blood Tests. Interleukin-6, 1,25-dihydroxyvitamin D (1,25-OH₂ D), and 25-OH D were analysed from blood taken after an overnight fast and a minimum of 18 hours after the last training session.

Plasma IL-6 was analysed using an ECLIA kit (Roche Diagnostics GmbH, Germany). According to the manufacturer, the limit of detection for this kit was 1.5 pg/mL, and the kit has been found to show no cross-reaction with such substances as IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-8, IFN- γ , and TNF- α . The analyses were performed at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark.

Serum 25-OH D was analysed using an immunological method that measures both vitamin D 3 and D 2 [18]. Analyses were performed at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark. The lower limit of detection for this analysis was 10 nmol/L. D vitamin status was categorized as being either normal (25-OH D \geq 50 nmol/L) or deficient (25-OH D < 50 nmol/L)

according to the KDIGO guidelines of 2012 [19]. Albumin, haemoglobin, C-reactive protein (CRP), and bicarbonate tests were collected from the patients' clinical practice and were analysed in the laboratories of the hospitals comprising those servicing the Capital Region.

2.5. Statistical Analyses. Data distributions were tested using a Shapiro-Wilk Test. In analyses of variables with nonnormal data distributions nonparametric statistics were used. Binary correlations were tested using the Spearman Test. The Wilcoxon Signed Ranks Test or paired Student's *t*-test was used to test for differences between the baseline test and pretraining and between pre- and posttraining and also to compare the differences during the control period with any difference during the training period. The Mann-Whitney Test or unpaired Student's *t*-test was used to compare groups of patients. Age adjustments were performed using linear and logistic regression, and entered analyses and variables were log-transformed if the residuals were not normally distributed. Data are presented as the mean \pm standard error of the mean (SEM), count, or percentages. All tests were two-tailed at a significance level of $P \leq 0.05$.

3. Results

Thirty-six patients were included and 23 patients completed the intervention. Six patients dropped out during the control period and three patients dropped out during the training period due to problems not related to training. Four patients completed the intervention but were not retested due to illness, change of dialysis modality, or problems arising during blood sampling. Two patients were not included in the IL-6 measurements and one patient was not included in the 25-OH D measurements owing to insufficient plasma collection.

Clinical characteristics are presented in Table 2. There was no gender difference for IL-6 (females 8.0 ± 2.5 versus males 9.0 ± 1.4 pg/mL, $P = 0.290$). Interleukin-6 was positively correlated with age ($r = 0.458$, $P = 0.006$) and CRP ($r = 0.693$, $P = 0.001$). At baseline, 51% of the patients were vitamin D deficient. There was no gender difference for 25-OH D (female 62.0 ± 10.1 versus male 59.1 ± 7.6 nmol/L, $P = 0.987$).

Clinical data in patients with reduced or elevated IL-6 values (split on the median 6.49 pg/mL) are presented in Table 3. Patients with elevated IL-6 values (≥ 6.49 pg/mL) were significantly older, ingested fewer grams of protein-day⁻¹·kilo⁻¹ body weight, and had impaired muscle power compared to those with reduced IL-6 values. When muscle power was age and gender adjusted, low muscle power in the left leg remained associated with elevated IL-6 values ($P = 0.042$), whereas impaired muscle power in the right leg tended to be associated with elevated IL-6 values ($P = 0.082$).

Mean IL-6 remained stable throughout the control and training period (Table 5). When the patients were split on the IL-6 median prior to training (7.4 pg/mL), reduced baseline IL-6 values (4.8 ± 0.5 pg/mL) and elevated baseline IL-6

TABLE 2: Baseline characteristics of the participants.

Parameter	Initial cohort <i>n</i> = 36
Age (years)	54 ± 2
Gender (f/m)	15/21
Duration of chronic dialysis (years)	5.4 ± 0.9
Dialysis modality (HD/PD)	30/6
Body mass index (kg/m ²)	25.0 ± 0.9
Albumin (g/L)	41.2 ± 0.6
Haemoglobin (mmol/L)	7.4 ± 0.2
C-reactive protein (mg/L)	7.2 ± 1.2
Bicarbonate (mmol/L)	25.7 ± 0.6
Comorbidities (score 0–3)	2.3 ± 0.1
Primary renal disease	
T2DM	1
Hypertension	4
Polycystic	8
Glomerulonephritis	14
Nephrosclerosis	2
Other/unknown	6
Interleukin-6 (pg/mL)	8.6 ± 1.3
1,25-OH ₂ D (pmol/L)	31.4 ± 1.8
25-OH D (nmol/L)	60.3 ± 6.0
Normal vitamin D, 25-OH D ≥ 50 nmol/L	49% (<i>n</i> = 17)
Mild vitamin D deficiency, 25-OH D 25–50 nmol/L	34% (<i>n</i> = 12)
Moderate vitamin D deficiency, 25-OH D 12.5–25 nmol/L	14% (<i>n</i> = 5)
Severe vitamin D deficiency, 25-OH D < 12.5 nmol/L	3% (<i>n</i> = 1)

F: female; M: male; HD: haemodialysis; PD: peritoneal dialysis. Data are presented as the mean ± SEM, count, or as a percentage.

values (21.9 ± 4.8 pg/mL) were unchanged after the training period (data not shown).

The IL-6 values tested prior to and during the training period did not correlate with changes in muscle power or muscle morphology during the training period (data not shown).

Plasma albumin was elevated in patients with normal 25-OH D compared to those with vitamin D deficiency (Table 4). Patients with normal 25-OH D had a reduced percentage of type 2X muscle fibres and an increased type 1 muscle fibre size. When 25-OH D was age and season adjusted, normal 25-OH D correlated with the reduced percentage of type 2X muscle fibres (*P* = 0.012) and a reduction in type 1 muscle fibre size (*P* = 0.013).

25-OH D was decreased after the training period (Table 5). In Figure 1, 25-OH D changes in the control and training period were stratified according to summer (April to September) and winter (October to March) periods. During the control and training periods, 25-OH D changed according to the season: during the summer, 25-OH D increased, and during the winter, the 25-OH D values decreased.

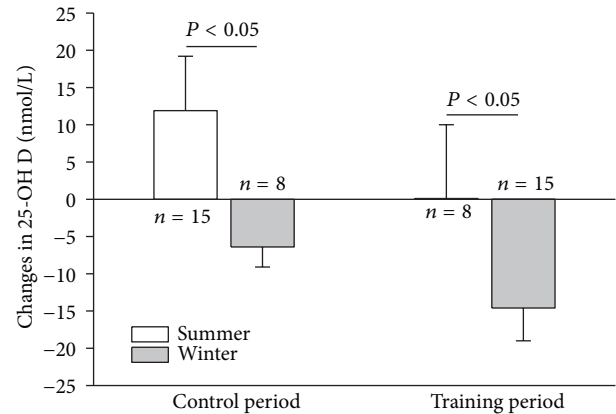


FIGURE 1: Changes in 25-OH D during the control period and the training period.

The 25-OH D status before and during the training period was not associated with changes in muscle power or muscle morphology during the training period (data not shown). However, decreased 25-OH D during the training period was correlated with an increase in the size of type 2 muscle fibres (*r* = -0.582, *P* = 0.009).

As previously shown, muscle power remained unchanged during the control period and increased during the training period (left leg from 2.01 ± 0.21 to 2.48 ± 0.20 W/kg, *P* < 0.001, and right leg from 2.11 ± 0.20 to 2.64 ± 0.19 W/kg, *P* < 0.001) [12]. Physical function determined by the Chair Stand Test remained also unchanged during the control period (from 15.2 ± 1.0 to 15.4 ± 1.3 repetitions, *P* = 0.164) and increased during the training period (to 18.7 ± 1.7 repetitions, *P* < 0.001) [12]. Muscle power changes during the training period were not correlated with IL-6 or 25-OH D (data not shown). As shown previously [20], mean muscle fibre size was not changed significantly between the pretraining and the posttraining tests (type 1: 4216 ± 311 versus 4427 ± 392 μm² and type 2: 3185 ± 233 μm² versus 3606 ± 275 μm², resp.). Body weight increased during the training period from 72.8 ± 3.7 to 73.9 ± 3.8 kg, *P* = 0.05.

4. Discussion

The main finding in this study was that 16 weeks of resistance training did not affect the level of the circulating proinflammatory cytokine IL-6 in a well-nourished sample of dialysis patients with relatively high values of plasma albumin. In cross-sectional analyses an elevated level of IL-6 was associated with impaired muscle power and a reduced protein intake. In addition, half of the patients were found to be suffering from vitamin D deficiency.

The IL-6 mean value was comparable with values reported in other studies focusing on skeletal muscle and exercise training in dialysis patients [21, 22]. In this study, patients with the most pronounced elevation of IL-6 had reduced muscle power, whereas no difference was found in muscle fibre size in-between patients with elevated or reduced IL-6 levels. Furthermore, an elevated IL-6 level was not found to affect the lack of muscle hypertrophy

TABLE 3: Baseline: interleukin-6 split on the median alongside the age, nutritional status, muscle function, and muscle morphology of the participants.

Variable	IL-6 < 6.49 (pg/mL) (n = 17)	IL-6 ≥ 6.49 (pg/mL) (n = 17)	P
N	17	17	
Age (years)	49.0 ± 3.4	61.2 ± 2.8	0.024
Gender, male (%)	52.9	64.7	0.486
Albumin (g/L)	42.2 ± 0.9	40.1 ± 0.7	0.068
Energy intake (kcal/kg/day)	2345 ± 132	2220 ± 150	0.710
Protein intake (g/kg/day)	1.49 ± 0.09	1.15 ± 0.11	0.019
Muscle power			
Leg extension, left (W/kg)	2.37 ± 0.20	1.42 ± 0.11	<0.001
Leg extension, right (W/kg)	2.43 ± 0.21	1.59 ± 0.11	0.002
Muscle fibre type			
Type 1 (%)	48.4 ± 3.3	46.5 ± 4.9	0.747
Type 2A (%)	36.3 ± 2.9	37.2 ± 3.1	0.826
Type 2X (%)	15.3 ± 3.5	16.3 ± 3.7	0.935
Muscle fibre size			
Type 1 (μm ²)	4406 ± 348	4610 ± 320	0.567
Type 2 (μm ²)	3526 ± 277	3270 ± 257	0.504

Data are presented as the mean ± SEM or as a percentage.

TABLE 4: Baseline: 25-OH D status and age, gender, nutritional status, glucose tolerance, muscle power, and muscle morphology for the participants.

Variable	Normal 25-OH D (≥50 nmol/L)	25-OH D deficiency (<50 nmol/L)	P
N	17	18	
Age (years)	51 ± 4	55 ± 4	0.525
Gender, male (%)	52	61	0.684
Tested during a summer period (%)	55.6	75.0	0.236
Albumin (g/L)	42.8 ± 0.7	40.1 ± 0.8	0.008
Energy intake (kcal/kg/day)	32.1 ± 2.8	29.9 ± 1.9	0.750
Protein intake (gr/kg/day)	1.39 ± 0.14	1.35 ± 0.10	0.512
Muscle power			
Leg extension, left (W/kg)	2.0 ± 0.3	2.0 ± 0.2	0.216
Leg extension, right (W/kg)	2.0 ± 0.3	2.2 ± 0.2	0.379
Muscle fibre type			
Type 1 (%)	46 ± 4	45 ± 5	0.491
Type 2A (%)	45 ± 3	33 ± 3	0.053
Type 2X (%)	9 ± 2	22 ± 4	0.022
Muscle fibre size			
Type 1 (μm ²)	4071 ± 256	5000 ± 366	0.048
Type 2 (μm ²)	3783 ± 276	3397 ± 266	0.950

Data are presented as correlation coefficients, the mean ± SEM, or a percentage.

TABLE 5: Interleukin-6 and 25-hydroxyvitamin D (25-OH D) levels for patients during the study.

Variables	Baseline	Pretraining	Posttraining	P control period	P training period	P in-between periods
IL-6 (pg/mL)	8.8 ± 1.9	14.5 ± 3.3	13.0 ± 3.6	0.063	0.394	0.289
25-OH D (nmol/L)	62.5 ± 8.4	69.1 ± 7.4	59.2 ± 7.5	0.145	0.038	0.167

Data are presented as the mean ± SEM (n = 23). The control period was between baseline and pretraining; training period was between pre- and posttraining.

after training in this study. However, a previous study has suggested that low-grade inflammation disturbs the balance between protein breakdown and synthesis and is thereby associated with muscle size in dialysis patients [21]. The lack of muscle hypertrophy after the present resistance-training program may be the result of several disturbing conditions including low-grade inflammation. Uraemia [23], dialysis *per se* [24], insulin resistance [25], anabolic hormone deficiency [26], and acidosis [27] are factors that contribute to a negative protein balance making the catabolic mechanism multifactorial. Thus, even though an elevated IL-6 level was not found to be a limiting factor in this study, it may still play a role in combination with other factors in the catabolism of muscle in dialysis patients.

The literature reports that exercise training may decrease elevated levels of circulating IL-6 in subjects without CKD [5, 28, 29] and in patients with CKD prior to dialysis [30]. Thus, we hypothesized that resistance training would decrease elevated IL-6 in dialysis patients. Whilst the mean value of IL-6 in all patients remained unchanged after training, this was also true for the subgroup of patients with the highest IL-6 levels. The fact that IL-6 levels were unchanged after the resistance training in our patients is supported by two other trials on dialysis patients [22, 31]. However, a potential response of exercise training in terms of a decrease in IL-6 may depend on training modality, dose, and intensity [28]. Whilst resistance training was used in the present and the two other previously mentioned studies [22, 31], a pilot study tested the effect of aerobic exercise on inflammation in patients treated with dialysis and also found IL-6 to be unchanged [32]. Based on the present and previous results [22, 31, 32], we find no reason to believe that exercise training is effective in combating elevated IL-6 values in dialysis patients. However, we cannot exclude that a higher dose of training could be effective and future studies may change the present conclusions. On the other hand, the lack of effect of exercise on IL-6 may be explained by the origin of the low-grade inflammation. As CKD and the dialysis treatment are important contributors to low-grade inflammation [33], effects of exercise training on IL-6 may not be possible to achieve in this patient group due to the nature of the chronic disease and the indispensable dialysis treatment.

It is well documented that exercise induces acute increased levels of circulating IL-6, which is stimulated by contracting muscle [5, 28]. Interleukin-6 therefore not only is a cytokine but also is recognized as a myokine with an anti-inflammatory capacity [5]. In the present study it is unknown as to whether the posttraining levels of IL-6 were affected by any acute rise after the training sessions. However, as the lowest IL-6 values also remained unchanged after the training period, an acute effect of exercise training on IL-6 seems likely not to have affected the results.

Vitamin D values were in line with data reported in other studies on dialysis patients [6, 7, 9, 34]. Half of the patients were suffering from vitamin D deficiency. The 25-OH D values changed according to the season and may likely be the result of an increase in exposure to sunlight. The seasonal changes of 25-OH D were anticipated based on a previous finding [34].

Vitamin D deficiency in CKD patients is treated to prevent secondary hyperparathyroidism and osteomalacia. In addition, treatment with 1,25-dihydroxyvitamin D has in a retrospective cross-sectional study been suggested to be associated with greater muscle size and muscle strength in dialysis patients [10]. However, as the authors did not report any vitamin D data and only presented the patients as being treated or not with vitamin D, it is unknown if the vitamin D values were correlated with muscle size and strength. One such connection was not supported by the results from our study. Furthermore, it has also been suggested that vitamin D status in dialysis patients is associated with the level of physical activity [34]. In this study 25-OH D decreased during the resistance training period, which might be explained by a seasonal impact. However, resistance training did not hinder the decrease in 25-OH D and we find no reason to suggest a positive effect of physical activity on vitamin D status in this patient group. One interesting finding, however, was that even though 25-OH D decreased during the training period, the patients were able to increase their muscle power significantly. Furthermore, we found an unexpected significant correlation between a decrease in 25-OH D and an increase in type 2 muscle fibre size during the training period. Thus, a decrease in 25-OH D during a resistance training period did not limit positive changes in muscle power, physical function, nor muscle hypertrophy in dialysis patients.

These results are limited, however, by the relatively low number of patients. In relation to the data for muscle size, estimations of muscle mass in the lower extremities determined by scanning methods would have been relevant in addition to a measure of muscle size at the fibre level. Scanning methods could have provided additional information of whole leg muscle mass and intramuscular fat content as relevant outcomes in this study.

In conclusion, in a well-nourished sample of dialysis patients, elevated serum IL-6 values were not decreased by a period of resistance training. Half of the patients were found to be suffering from vitamin D deficiency. The low-grade inflammation was associated with reduced muscle power but not with muscle fibre size. Elevated IL-6 values and vitamin D deficiency did not affect the positive effects of resistance training on muscle power and physical function.

Conflict of Interests

Pia Eiken is an advisory board member with Amgen and MSD and registered with the speaker's bureau for both Amgen and Eli Lilly.

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Clinical Study

Physical Performance Is Associated with Working Memory in Older People with Mild to Severe Cognitive Impairment

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Background. Physical performances and cognition are positively related in cognitively healthy people. The aim of this study was to examine whether physical performances are related to specific cognitive functioning in older people with mild to severe cognitive impairment. **Methods.** This cross-sectional study included 134 people with a mild to severe cognitive impairment (mean age 82 years). Multiple linear regression was performed, after controlling for covariates and the level of global cognition, with the performances on mobility, strength, aerobic fitness, and balance as predictors and working memory and episodic memory as dependent variables. **Results.** The full models explain 49–57% of the variance in working memory and 40–43% of episodic memory. Strength, aerobic fitness, and balance are significantly associated with working memory, explaining 3–7% of its variance, irrespective of the severity of the cognitive impairment. Physical performance is not related to episodic memory in older people with mild to severe cognitive impairment. **Conclusions.** Physical performance is associated with working memory in older people with cognitive impairment. Future studies should investigate whether physical exercise for increased physical performance can improve cognitive functioning. This trial is registered with ClinicalTrials.gov NTR1482.

1. Introduction

In healthy older people a high level of physical activity coincides with a high level of cognitive performance, such as speed of information processing, attention [1], and executive functions (EF) [2]. The results of those studies are in line with the finding that a high level of physical activity during life might decline the risk of dementia [3]. Since physical activity also increases *physical performance*, such as muscle strength, gait speed, functional mobility, and balance [4], it is not surprising that there is a positive relationship between physical performance and cognition in healthy older people [5]. More specifically, older people with better physical performance levels, for example, mobility [6], balance [7], strength [6, 8], and aerobic fitness [9], have better cognitive functions, such as cognitive flexibility or global cognition. Moreover, similar to physical activity, better physical performance, such as balance [7] and strength [8, 10], also decreases the risk of dementia [11].

The studies mentioned above suggest a close relationship between physical performance and cognitive functioning in cognitive healthy older people. In older adults with amnesic mild cognitive impairment (aMCI) [12] or mild dementia [13], this relationship is further strengthened. In people with aMCI, gait speed and the performance on the Timed Up and Go (TUG) were both associated with EF [12], which are higher cognitive functions, such as working memory, supported by the prefrontal cortex (PFC) [14]. It is even suggested that particularly EF, as opposed to global cognition or memory, is important for mobility performances, such as balance, gait [15], and the ability to perform the activities of daily life (ADL) [16]. This suggestion was supported by a positive relationship between gait and EF in a combined group of cognitive healthy young elderly and elderly with and without mild dementia [17].

Not only is gait affected in an early stage of dementia [13, 18–20], but also there is increasing evidence for a decline in lower-extremity functioning, for example, walking speed

[19], balance [18, 20], fine and complex motor functioning [21], aerobic fitness [22], and limb coordination [20], already in an early stage of dementia. When people have dementia in a relatively early stage, balance stays an independent predictor of the progression in (further) global cognitive decline [23]. The studies above, which included people with dementia, show only a relation between physical performance and the stage or progression of the dementia, not with specific cognitive functions. In addition, these studies often include only specific types of dementia or only people in, for example, a mild stage of dementia, and often did not control for the level of depression, even though this can influence the level of cognition [24].

The goal of the present study was to examine if physical performance (strength, balance, mobility, and aerobic fitness) is related to specific cognitive functions in people with mild to severe cognitive impairment. If this appears to be the case, therapeutic interventions specifically aimed at maintaining or improving one or more physical performances might be useful to slow down a decline or even to improve cognitive functioning in cognitively impaired older people.

2. Methods

The present cross-sectional study includes baseline data of a longitudinal randomized controlled trial (RCT) examining the effect of physical activity on, among others, physical performance and cognition (for details, see [25]). Participants were recruited via medical staff of aged care facilities. Firstly, the medical staff was informed about the goal and procedure of the RCT. Secondly, possible participants were selected within subunits of the institutions. Thirdly, an information letter with informed consent was sent to the legal representatives of the selected participants. Fourthly, once written consent was received, participants were tested for inclusion and exclusion criteria.

2.1. Participants. One hundred and thirty-four participants (96 women), 82.2 ± 7.4 years old, with cognitive impairment participated in this study. However, due to missing values, 47 participants could not be analysed (see Figure 1). The severity of the cognitive impairment was determined by the Mini-Mental State Examination (MMSE), a test to measure global cognitive functioning, that is, orientation in time and place, word recall, attention and calculation, language abilities, and visuospatial ability (scores range from 0 to 30) [26]. Eligibility criteria for study participation were the presence of cognitive impairment ($\text{MMSE} < 25$) and being ambulatory with or without walking aid (walker or cane). Exclusion criteria were the presence of personality disorders, cerebral traumata, hydrocephalus, neoplasm, disturbances of consciousness, and focal brain disorders. Characteristics of participants are shown in Table 1.

2.2. Level of Depression. The level of depression was based on the summed standardized scores of Geriatric Depression Scale (GDS) and Symptoms Checklist 90 (SCL-90) (Cronbach's Alpha is 0.91).

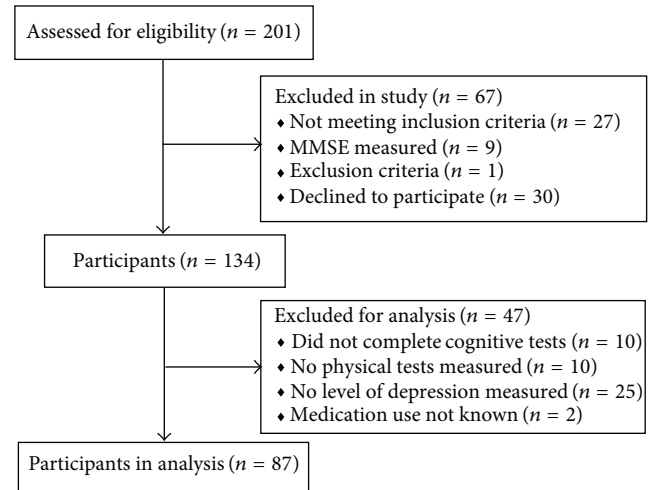


FIGURE 1: Flowchart of participants.

GDS. The Dutch version [27] of the GDS is a 30-item questionnaire used to measure general mood [28]. The GDS is a reliable and valid self-rating depression screening scale for elderly populations [29]. The GDS questions are answered by “yes” or “no” depending on which response is most appropriate at the time of measurement, with 0 or 1 point for each answer. Higher scores indicate a higher level of depression with a maximum score of 30.

SCL-90. One subscale from the Dutch version [30] of the SCL-90, a 90-item self-report symptom inventory designed to reflect patterns of current psychological symptoms, was used to measure depression [31, 32]. The depression subscale includes 15 items. Each item is rated on a 5-point likert scale, from 1 (not at all) to 5 (extremely). A higher score indicates more symptoms of depression with a maximum score of 75.

2.3. Education. The highest education level was determined on a seven-point scale with 1 = less than elementary school to 7 = university and technical college [33].

2.4. Comorbid Conditions. Comorbid conditions (see Table 1) were extracted from the medical status and categorized based on the Dutch translation of the Long-Term Care Facility Resident Assessment Instrument (RAI), section I. This section (disease diagnoses) includes the following categories: (1) endocrine/metabolic/nutritional, (2) heart/circulation, (3) musculoskeletal, (4) neurological, (5) sensory, (6) psychiatric/mood, (7) pulmonary, and (8) others. The total sum of 8 categories was used as a comorbidity score.

2.5. Medication Use. Medication use (see Table 1) is coded according to the Dutch Pharmacotherapeutic Compass and is ranged by the following groups: (1) antipsychotics, (2) antidepressants, (3) psychotropics (central nervous system (CNS)), (4) neurological (CNS), (5) anaesthetics and muscle relaxing, (6) blood, (7) cardiovascular, (8) gastrointestinal tract, (9) respiratory tract, (10) kidneys and urinary tract,

TABLE 1: Demographics and characteristics of participants.

	Total participants (<i>n</i> = 134)		Participants in analysis (<i>n</i> = 87)		Participants not in analysis (<i>n</i> = 47)		Test statistics	
	mean	SD	mean	SD	mean	SD	<i>t</i>	df
Demographics and characteristics								
MMSE (0–30)	15.4	5.9	17.4	4.8	11.6	6.1	−5.66**	132
Age (years)	82.2	7.3	82.5	7.1	81.4	7.8	−0.84	132
Education (1–7)	3.4	1.5	3.4	1.4	3.4	1.7	0.12	127
Gender (% women)	71.6		75.9		63.8		2.18 ^x	1
GDS (0–30)	7.2	5.5	7.1	5.7	8.5	3.7	0.85	96
SCL-90 (0–75)	21.1	6.5	21.0	6.6	21.4	5.1	0.17	94
BMI (kg/m ²)	26.9	4.4	27.2	4.3	26.3	4.5	−1.01	115
Medication use (0–26)	4.7	2.5	4.6	2.5	5.0	2.4	0.81	129
Comorbidities (% with disease)								
Endocrine/metab/nutr	24.2		26.4		20.0		0.67 ^x	1
Heart/circulation	65.2		66.7		62.2		0.26 ^x	1
Musculoskeletal	37.9		41.4		31.1		1.33 ^x	1
Neurological	97.0		96.6		97.8		0.15 ^x	1
Sensory	24.2		26.4		20.2		0.67 ^x	1
Psychiatric/mood	24.2		25.3		22.2		0.15 ^x	1
Pulmonary	9.8		9.2		11.1		0.12 ^x	1
Other	30.3		29.9		31.1		0.02 ^x	1

Notes: Test statistics show differences between participants in analysis and participants not in analysis; df: degrees of freedom; *t*: independent *t*-test; ^x χ^2 test; * *P* value < 0.05; ** *P* value < 0.01.

BMI: Body Mass Index; GDS: Geriatric Depression Scale; metab: metabolic; MMSE: Mini-Mental State Examination; nutr: nutritional; SCL-90: Symptoms Checklist 90.

(11) genital tract, (12) dermatology, (13) otolaryngology, (14) ophthalmologic, (15) infectious diseases, (16) hormones and bone metabolism, (17) analgesics, antirheumatic drugs and gout agents, (18) vitamins and minerals, (19) malignancies, (20) infectious diseases, (21) various preparations, (22) dentistry, and (23) opioids. The total of all 23 categories was used as medication score.

2.6. Informed Consent. The Medical Ethical Committee of VU university medical center approved the longitudinal study. Before the baseline measurement, participants or their caregivers provided written informed consent for the longitudinal study.

3. Outcome Variables

To assess physical performance and cognitive functioning, the following tests were administered.

3.1. Assessment of Physical Performance

3.1.1. Mobility. The mobility performance was computed by three physical tests, that is, the Ten Meter Timed Walk, Figure of Eight, and the TUG (Cronbach's alpha = 0.86). For final mobility, the performance was multiplied by −1, where higher scores indicate better mobility.

Ten Meter Timed Walk. Participants are requested to walk 10 meters at their own regular pace between 4 small traffic cones, which are placed in the corners of a 10 by 1 meter rectangle [34]. The time to walk 10 meters is measured by hand with a stopwatch to the nearest of 1/10 of a second.

Figure of Eight. The Figure of Eight is an applicable and reliable dynamic functional balance measure of mobility for people with various degrees of physical disability [35] and geriatric patients [36]. The Figure of Eight test requires continuous turning with an emphasis on accuracy (avoid oversteps), speed (timed task), and switching of motor patterns during the crossover from the clockwise to the counterclockwise loop. Participants are timed while walking in a figure-8 trajectory. The figure-8 trajectory is marked with white paint on a dark green rubber carpet, each loop having an outer diameter of 165 centimetres (cm) and a step width of 15 cm. The time to walk two complete eight figures is measured with a stopwatch. The onset time is based on the first detectable movement of the participant following a "Go!" command from the observer. Any step taken outside the white line is noted. The fastest attempt of two trials is recorded together with the corresponding oversteps.

TUG. The TUG is a reliable and valid test for quantifying functional mobility that may also be useful in following

clinical change over time [37]. To complete the TUG, participants are requested to rise from a standard chair (48 cm height, horizontal seat with armrests), walk 3 meters, turn around, and return to a fully seated position in the chair again [38]. Each participant has two trials and the average time in seconds is the outcome of the TUG.

3.1.2. Strength

Sit To Stand (STS). The STS is normally a reliable and valid indicator of lower body strength in adults over 60 years [39]. However, in this study, participants are allowed to use upper limbs to rise from the chair to test their rising performance that is closest to the clinical setting and to reduce a floor effect; a high percentage of older dependent elderly cannot rise from a chair with the arms crossed in front of the chest [40]. Participants are instructed to stand up and sit down in a standard chair as many times as possible within 30 seconds. The STS score is formed by the total number of performances with a sit-stand-sit performance counting as 1. Ending in a standing position is counted by a 0.5 point.

3.1.3. Aerobic Fitness

Six-Minute Walk Test (6MWT). The 6MWT can be used reliably in the assessment of functional endurance ambulation in persons with acquired brain injury [41]. During the performance of the 6MWT, participants are instructed to cover as much distance as possible during 6 minutes with the opportunity to stop and rest if necessary [42]. Participants have to walk around a premeasured, unobstructed 10 by 1 meter rectangular circuit having semicircular ends with 0.5 meter radii marked out with plastic cones to prevent participants having to walk at sharp angles. One full round covers 26.3 meters walking. The total walking distance by each participant will be measured to the nearest meter.

3.1.4. Balance

Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT-4). The FICSIT-4 is a test to measure static balance [43]. The participants have to maintain balance in 4 positions with increasing difficulty. Each position is demonstrated first and support is offered while participants position their feet. When participants are ready, the support will be released and timing begins. The timing stops when participants move their feet or grasp the researcher for support, or when 10 seconds have elapsed. Only when one position is performed for 10 seconds, the next, more difficult position is performed. The first position is with the feet together in parallel (side-by-side) position. Second is the semitandem position: the heel of one foot is placed to the side of the first toe of the other foot. The participant can choose which foot to place forward. Third is a tandem position: the heel of one foot directly in front of the toes of the other foot. The final position is standing on one leg. The total summed seconds of the performed positions are the outcome score.

3.2. Assessment of Cognitive Functioning. Besides the MMSE, 13 neuropsychological tests were administered, but 6 tests, that is, Digit Span forward, Visual Memory Span forward, Rule Shift Cards, Key Search, Picture Completion, and the Stroop test (for details, see [25]), were not analyzed in this study, because these tests could not be included in a specific cognitive domain. Four tests, that is, the Digit Span backward and Visual Memory Span backward, Category Fluency tests, and the Digit Symbol Substitution Test (Cronbach's $\alpha = 0.82$), could be included into one domain, that is, working memory (for processing information), one of the EF. Furthermore, 3 tests, that is, the Eight Words test and Face Recognition and Picture Recognition (Cronbach's $\alpha = 0.75$), could be combined to compose an episodic memory domain (for learning new information).

3.3. Working Memory

Digit Span Backward. The Digit Span is a subtest from the Wechsler Memory Scale-Revised (WMS-R) [44]. In the Digit Span backward, increasingly long sequences of random numbers are orally presented at a rate of one digit per second to the participants, who have to repeat the sequence in reverse order immediately after oral representation. This condition ends when a participant fails to recall at least two strings of the same length or repeats an eight-digit sequence correctly. The minimal score for this conditions is 0 and the best score is 21.

Visual Memory Span Backward. The Visual Memory Span is a subtest of the WMS-R [44]. The Visual Memory Span backward stimuli consist of squares printed on a two-dimensional card and requires the participant to repeat a number of tapping sequences in reverse order, similar to the Digit Span backward. This test is used as a measure of visual working memory [44]. Scores range from 0 (worst) to 12 (best).

Category Fluency Test. The Category Fluency test is a verbal fluency test which can be used to evaluate working memory [45]. The participant is asked to name as many examples of a given category as possible, within 1 minute. This study uses the category "animals" and "professions" [46]. The outcome measure is the total number of animals and professions produced.

Digit Symbol Substitution Test (DSST). The DSST is a subtest of the WAIS-Revised [44]. Test scores correlate with general intelligence, cognitive impairment, chronological age, and activation in the frontal regions [47–49]. Participants are presented with a rectangular grid of numbers. For each of these numbers, participants are instructed to substitute the appropriate symbol according to a code that appears at the top of the page. The DSST score is recorded as the number of correct symbols drawn in 2 minutes.

3.4. Episodic Memory

Eight Words Test. The Eight Words test is a list-learning test for people with memory problems [50]. In this test,

the examiner reads out eight words in a row, which is repeated five times. Every time the participant is asked to recall as many words as possible. The first outcome measure is the total number of correctly recalled words after the five trials (*immediate recall score*, maximal score = 40). After an interval of approximately 15 minutes, the participant is asked to recall as many words as possible (*delayed recall score*, maximal score = 8). Subsequently, the examiner reads aloud 16 words among which 8 words presented before and 8 new words. The participant is asked to recognize the words from the list presented before (*recognition score*, maximal score = 16).

Face Recognition. Face Recognition is a subtest from the Rivermead Behavioral Memory Test (RBMT) [51] and measures visual, nonverbal long-term memory. Two versions (C+D) are combined to prevent a ceiling effect. In this test, the participant is shown 10 cards with faces one at a time for 5 seconds. After a short interval of approximately 2 minutes, the participant is shown 20 cards, including 10 shown before and 10 cards with new faces. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of faces correctly recognized minus the number of faces incorrectly recognized. The worst score is -20 and the best score is +20.

Picture Recognition. Picture Recognition is also a subtest from the RBMT [51], which measures visual, verbal long-term memory. Two versions (C+D) are combined to prevent a ceiling effect. The participant is shown each of the 20 cards with drawings of objects for 5 seconds. With each card, the participant is requested to name the object on the card. After a short interval of approximately 2 minutes, the participant is shown 40 cards, including 20 shown before and 20 cards with new objects. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of objects correctly recognized minus the objects that were incorrectly recognized. The lowest score is -40 and the maximal score is +40.

4. Data Analysis

The data was analyzed using *Statistical Package for the Social Sciences* (SPSS) version 16.0 (SPSS, Inc., Chicago, IL). For data reduction, scores on neuropsychological tests and physical performances were converted into standardized z-scores to receive equal weighting towards a combined domain. With principal component analysis, eigenvalues >1, at least a good internal consistency of the domain (Cronbach's alpha at least 0.70), 2 cognitive domains, and 1 physical performance domain could be developed by summing up the z-scores. The 3 other physical performances were based on 1 test. Hierarchical multiple regression analysis involved four steps. We tested the hypothesis that a physical performance (mobility, balance, strength, or aerobic fitness) would be a significant predictor of cognitive functioning (working memory or episodic memory) (Step 3) after controlling for age, education, depression, comorbidities, medication use (Step 1), and cognitive impairment (MMSE) (Step 2). The significance of the increment in the squared multiple

correlation was tested when the physical performance was entered after the control variables. Furthermore, to analyze whether the physical performance as a predictor was different for people in different stages of cognitive impairment, we added the interaction (MMSE \times physical performance) to the model (Step 4). A two-sided P value < 0.05 was considered statistically significant.

5. Results

The results of the hierarchical multiple regression analysis with working memory and episodic memory as dependent variables, controlling for age, education, depression, comorbidity, medication (Step 1), MMSE (Step 2), the physical performance (Step 3), and interaction between physical performance and MMSE (Step 4) as predictors are shown in Table 2.

5.1. Working Memory. *Balance, strength, and aerobic fitness* (Step 3) are all significantly associated with working memory ($P < 0.05$) after controlling for covariates and the level of global cognition. Each performance explains 3% to 7% of the total variance of working memory, irrespective of the level of cognitive impairment (Step 4 not significant).

5.2. Episodic Memory. *Mobility, balance, strength, and aerobic fitness* (Step 3) are not significantly related to episodic memory ($P \geq 0.05$) after controlling for covariates and the level of global cognition in older people with all levels of cognitive impairment (Step 4 not significant).

6. Discussion

Although physical performances, such as strength and mobility, are assumed to be related to cognition, for example, global cognition measured with 19 different neuropsychological tests [10] and EF [6, 12], our findings show that in people with mild to severe cognitive impairment, this is also true for working memory, but not for episodic memory. More specifically, the results indicate that the performance in *balance, strength, and aerobic fitness* is positively related to the performance in working memory, irrespective of the level of cognitive impairment.

6.1. Working Memory. *Strength, balance, and aerobic fitness* are significantly associated with working memory, an aspect of EF [14], in people with a mild to severe cognitive impairment. This association is independent of the number of comorbidities, age, level of depression, education level, and medication use. That *strength* (also measured with STS) is related to working memory/attention, measured by the Digit Span forward and backward, was also observed in older cognitively healthy women [52]. In contrast, in a combined group of cognitively healthy older men and women, knee extension strength was not related to working memory [6]. However, in that study working memory was assessed by only one neuropsychological test, that is, the Digit Span backward. In addition, knee extension strength was related to a Lexical

TABLE 2: Results of multiple regression analysis with physical performances as predictors (Steps 3 and 4) of working memory and episodic memory after controlling for age, education, level of depression, number of comorbidities, medication, and MMSE (Steps 1 and 2).

Dependent variable	Steps of analysis	Predictor	β	t	Cum R^2	Incr R^2
Working memory ($n = 86$)						
	Step 1	Age	-0.23	2.12*		
		Education	0.26	2.50*		
		Depression	-0.22	2.13*		
		Comorbidity	-0.04	0.29		
		Medications	-0.13	1.10	0.17	0.17*
	Step 2	MMSE	0.61	7.01**	0.49	0.32**
	Step 3	Mobility	0.08	0.77	0.49	0.00
	Step 4	MMSE * mobility	0.18	0.78	0.50	0.00
	Step 3	Balance	0.20	2.02*	0.51	0.03*
	Step 4	MMSE * balance	0.15	0.39	0.52	0.00
	Step 3	Strength	0.31	3.43**	0.56	0.07**
	Step 4	MMSE * strength	0.81	1.79	0.57	0.01
	Step 3	Aerobic fitness	0.21	2.02*	0.51	0.03*
	Step 4	MMSE * aerobic fitness	0.46	1.22	0.52	0.01
Episodic memory ($n = 87$)						
	Step 1	Age	-0.29	2.60*		
		Education	0.19	1.82		
		Depression	0.07	0.62		
		Comorbidity	0.05	0.36		
		Medications	0.06	0.46	0.12	0.12
	Step 2	MMSE	0.58	6.20**	0.40	0.29**
	Step 3	Mobility	-0.05	0.45	0.40	0.00
	Step 4	MMSE * mobility	-0.14	0.54	0.41	0.00
	Step 3	Balance	0.14	1.31	0.42	0.01
	Step 4	MMSE * balance	-0.54	1.31	0.43	0.01
	Step 3	Strength	-0.07	0.72	0.41	0.00
	Step 4	MMSE * strength	-0.40	0.76	0.41	0.00
	Step 3	Aerobic fitness	-0.00	0.02	0.40	0.00
	Step 4	MMSE * aerobic fitness	-0.34	0.81	0.41	0.01

Notes: β : standardized beta coefficient; Cum: cumulative; Incr: increase; MMSE: Mini-Mental State Examination; t : t statistic. * P value < 0.05; ** P value < 0.01.

Fluency test [6]. The latter test measures cognitive flexibility, which is in the current study included in the working memory domain by two Category Fluency tests [53]. In the current study, the Digit Span backward and two Category Fluency tests were only three out of five neuropsychological tests of a strong domain “working memory” (Cronbach’s alpha = 0.85). Overall, all of the measured working memory and cognitive flexibility tests mentioned above appeal to EF [25], and therefore *strength* seems to be related to EF and not only working memory.

In the present study, *mobility* was not significantly associated with working memory in people with a cognitive impairment. A possible reason why mobility is not related to working memory, while other physical measures are, is that mobility was performed at “regular pace” instead of “as fast as possible”, which probably causes a smaller difference in performance between participants. In cognitively healthy older people, the 4-meter timed walk test, which was also

performed at usual pace, was also not related to the Digit Span test (score of Digit Span backward minus the score on the Digit Span forward) in older women [54] nor was the mobility performance (measured with POMA) related to the Digit Span backward in older men and women [6]. In contrast, the mobility performance of the latter study was associated with fluency, a cognitive performance that we included in working memory. However, their mobility performances (measured with the POMA) included not only gait and mobility but also balance. Possibly balance caused the significant relation, since *balance* is also significantly associated with working memory in the present study. *Balance* is dependent on the functioning of the frontocerebellar and frontostriatal connections [13], connections between, respectively, the cerebellum and the striatum and the frontal cortex, for example, dorsolateral PFC (DLPFC) [13]. Since the DLPFC is also involved in working memory [55], it is not surprising that in people with a cognitive impairment, *balance* is significantly related to

working memory, because both performances appeal to the same neural circuits.

Aerobic fitness (measured with 6 MWT) is significantly associated with working memory in cognitively impaired older people. This was not observed in cognitively healthy older women [52]. However, the latter study measured a small number of participants ($n = 41$) and had a combined EF domain of working memory with attention. This combined domain was measured with the Digit Span backward and with the Digit Span forward, which is different from the current study. A mechanism underlying the present finding might be that *aerobic fitness* is associated with white matter volume, even after controlling for age, gender, dementia severity, physical activity, and physical frailty [22]. White matter volume is positively related to working memory [56]. Indeed, executive control processes, such as working memory, show the largest benefits of improved fitness in older people [56]. Clinically, working memory is essential for storing information, and therefore it is crucial for long-term memory and learning [57, 58]. However, working memory is vulnerable during aging and dementia [59]. To reduce a decline in working memory, results of this study suggest that it is important to maintain good balance, strength, and aerobic fitness. Indeed, in older people with mild Alzheimer's disease, balance and coordination exercises seem to improve working memory in a pilot study [60].

6.2. Episodic Memory. *Mobility, balance, strength, and aerobic fitness* are not related to episodic memory in people with mild to severe cognitive impairment. These nonsignificant results are not very surprising, since motor performances are highly related to PFC-related cognitive functions, for example, attention, EF, and working memory, and less with hippocampal cognitive functions, for example, episodic memory. Therefore, *aerobic fitness* interventions show the highest effect sizes on cognitive functions in which the PFC plays an important role [56]. However, a higher effect size does not imply that aerobic fitness is only related to PFC-related cognitive functions and not with hippocampal related cognitive functions. Indeed, a comparable study in older people with MCI has suggested that aerobic fitness may be the most important physical performance, besides strength, balance, and mobility, that is related to the volume of the hippocampus [61]; this has been confirmed in another study in people with (very) mild AD [62]. Because hippocampal volume is positively related to episodic memory [63], these studies suggest that aerobic fitness and episodic memory are associated with people with MCI and (very) mild AD. However, participants of both studies were not only 8 years younger than participants of the current study (74 versus 82 years), but they had less cognitive impairment as well, including also people with subjective cognitive impairment, with a mean MMSE of 27 [61] or 26 [62]; in the current study participants with a MMSE above 24 were excluded. With increasing cognitive impairment, the hippocampus and PFC are both more affected [64]. However, to encode items for episodic memory, the anterior medial PFC is activated as well [65]. This suggests that, in people with increasing cognitive

impairment, a high level of aerobic fitness, obtained by a high level of physical activity, has to improve the affected PFC first before an improvement in episodic memory can be observed. Therefore, we argue that the relationship between aerobic fitness and working memory (or EF) is stronger than the relationship between aerobic fitness and (episodic) memory in people with cognitive impairment. Indeed, in people with a decline in both working memory and episodic memory as is the case in obese older people [66], aerobic fitness was related to EF, but not to memory [67]. In cognitively healthy people with a well-functioning PFC, the relationship between aerobic fitness and episodic memory is more often observed [68–71]. As far as the authors know, there are no other comparable studies assessing the relation between specific physical performance and episodic memory in older people with objective mild to severe cognitive impairment.

6.3. Passivity. Physical performances can be increased by physical activities not only in cognitively healthy older people but also in people with a cognitive impairment [72]. Since physical performances are related to cognitive functioning, it is not surprising that cognitive functioning decreases faster in people with low levels of physical activity [73]. Regrettably, most elder community-dwelling people do not meet the recommended level of physical activity [74], which is at least 30 minutes of moderate intensity for 5 days per week in sessions of at least 10 minutes [75]. Cognitive functions decline even faster when people move into an institution, because of their low levels of physical activity [74]. Therefore, we need to consider the optimal timing and intensity of the physical activity, as well as the type of training, which should improve balance, strength, and aerobic fitness.

6.4. Limitation. A limitation of the present study is its cross-sectional design, implying that one can only report associations instead of a causal relationship. Longitudinal intervention studies are necessary to examine whether improvements in physical functioning also increase cognitive functioning, such as working memory.

Another potential limitation of our study is the composition of our study sample. Participants were recruited for a longitudinal RCT. Consequently, our sample may represent only participants who are willing to be randomised to an experimental or control group and are willing to attend multiple measurements. However, it was communicated that if participants were randomised into the control group, they were able to start the intervention at later moment, and that participants could refuse measurements at any time without reason.

7. Conclusion

In people with mild to severe cognitive impairment, the performances in balance, strength, and aerobic fitness are significantly associated with working memory, but not with episodic memory. Future studies should investigate whether physical exercise for increased physical performance can

improve cognitive functioning. For the best physical exercise, we need to consider the optimal timing and intensity of the physical exercise, as well as the type of training, which should improve balance, strength, and aerobic fitness.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

High versus Moderate Intensity Running Exercise to Impact Cardiometabolic Risk Factors: The Randomized Controlled RUSH-Study

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Aerobic exercise positively impacts cardiometabolic risk factors and diseases; however, the most effective exercise training strategies have yet to be identified. To determine the effect of high intensity (interval) training (HI(I)T) versus moderate intensity continuous exercise (MICE) training on cardiometabolic risk factors and cardiorespiratory fitness we conducted a 16-week crossover RCT with partial blinding. Eighty-one healthy untrained middle-aged males were randomly assigned to two study arms: (1) a HI(I)T-group and (2) a sedentary control/MICE-group that started their MICE protocol after their control status. HI(I)T focused on interval training (90 sec to 12 min >85–97.5% HRmax) intermitted by active recovery (1–3 min at 65–70% HRmax), while MICE consisted of continuous running at 65–75% HRmax. Both exercise groups progressively performed 2–4 running sessions/week of 35 to 90 min/session; however, protocols were adjusted to attain similar total work (i.e., isocaloric conditions). With respect to cardiometabolic risk factors and cardiorespiratory fitness both exercise groups demonstrated similar significant positive effects on MetS-Z-Score (HI(I)T: -2.06 ± 1.31 , $P = .001$ versus MICE: -1.60 ± 1.77 , $P = .001$) and (relative) VO_2max (HI(I)T: $15.6 \pm 9.3\%$, $P = .001$ versus MICE: $10.6 \pm 9.6\%$, $P = .001$) compared with the sedentary control group. In conclusion, both exercise programs were comparably effective for improving cardiometabolic indices and cardiorespiratory fitness in untrained middle-aged males.

1. Introduction

Higher levels of cardiorespiratory fitness are associated with lower risk of all causes of mortality and cardiovascular-/coronary heart diseases (CVD/CHD) [1]. Exercise significantly impacts cardiorespiratory fitness and is thus strongly recommended in both primary and secondary prevention of cardiometabolic diseases [2–4]. However, the most efficient exercise training strategies to positively affect cardiorespiratory fitness and cardiometabolic risk factors have yet to be identified. With respect to exercise intensity, there is some evidence that walking may be as effective as running for reducing cardiometabolic risk [5] at least when adjusting for energy expenditure (i.e., work). However, running is much more time efficient due to its higher physiological

and biomechanical intensity [6]. This aspect is substantial, since lack of time was consistently reported as one of the central reasons for inactivity in Germany [7]. Developing this idea further, low volume/high intensity protocols should be a promising tool for impacting cardiometabolic risk in sedentary subjects. In fact, a number of corresponding studies that focus on prevention or rehabilitation of metabolic and cardiac diseases including myocardial infarction [8] applied low volume/high intensity (interval) training (“HI(I)T”) [9–13]. Beside its apparent time effectiveness a main pro for HIIT is its significantly higher effect on VO_2max , the parameter considered as the typical marker of cardiorespiratory fitness [14], compared with “moderate intensity continuous exercise” (MICE) protocols traditionally applied in this research field

(review in [15–19]). Since most of these studies focus on subjects with severe CAD and/or heart failure (review in: [15–17, 19, 20]) exercising on electronically braked cycle ergometers, it is doubtful, whether these data are transferable to the general population. Comparative studies that address primarily prevention of CVD/CHD are scarce [9, 13, 21–24].

For that reason, the primary purpose of this randomized controlled trial is to compare the effects of two running exercise protocols (HIIT versus MICE) under the premise of comparable “energy consumption” on the Metabolic Syndrome (MetS) as a sensitive cluster of metabolic and cardiac risk factors in untrained middle-aged males.

The primary hypothesis was that HIIT is significantly superior for impacting the Metabolic Syndrome (MetS) Z-Score and the number of criteria of the MetS in this cohort. The secondary hypothesis was that HIIT is significantly more effective for increasing cardiorespiratory fitness compared with MICE.

2. Materials and Methods

The Running Study and Heart (RUSH) Trial was a 16-week randomized controlled crossover study with three study arms (two exercise, one waiting/control group) of untrained middle-aged males (Figure 1). The study was conducted by the Institute of Medical Physics, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Germany, during April 2011 and July 2012. The primary study aim was to compare the effects of a high intensity (interval) training protocol (HI(I)T) versus a moderate intensity continuous exercise protocol (MICE) on physical performance, metabolic, and cardiac parameters. The study protocol was approved by the ethics committee of the Friedrich-Alexander University (FAU) of Erlangen-Nürnberg (Ethikantrag 4463). All the study participants gave written informed consent. The study was registered under www.clinicaltrials.gov (NCT01406730).

2.1. Main Endpoints. The primary study endpoints of the present contribution were as follows.

- (i) Metabolic Syndrome (MetS) Z-Score according to Johnson et al. [25].
- (ii) Number of MetS parameters according to the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) definition [26].

Secondary study endpoints were as follows.

- (i) Maximum aerobic capacity ($\text{VO}_{2\text{max}}$)
- (ii) Metabolic Syndrome criteria constituting the NCEP ATP III MetS criteria (i.e., waist circumference, mean arterial pressure (MAP), fasting glucose, triglycerides, and HDL-C).

2.2. Study Participants, Inclusion, and Exclusion Criteria. Study characteristic procedures of recruitment and the flow chart of the trial were described in more details in an earlier publication [27]. In summary (Figure 4), detailed announcements in local newspapers or on radio stations

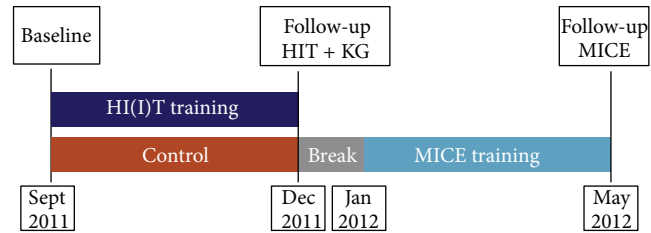


FIGURE 1: Time chart of the RUSH study.

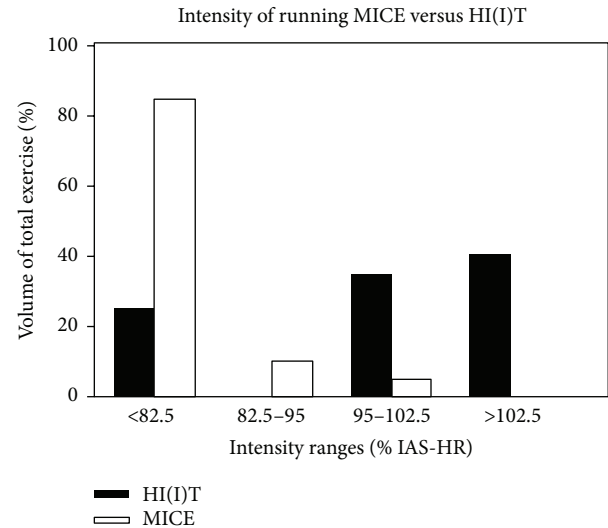


FIGURE 2: Exercise volume in different metabolic areas: HI(I)T versus MICE-running group. IAT: individual anaerobic threshold; HR: heart rate.

addressed untrained male subjects 30–50 years old. 121 subjects responded and were assessed for eligibility. Of these, 24 subjects had to be excluded due to the criteria of (a) male, 30–50 years old ($n = 3$), (b) “untrained” (i.e., ≤ 1 endurance exercise session/week; ≤ 2 total exercise sessions/week during the last 2 years; $n = 12$), (c) inflammatory diseases and pathological changes of the heart ($n = 3$), (d) medication/diseases affecting cardiovascular system, muscle, or joints/bone ($n = 1$), (e) <100 Watt at ergometry ($n = 0$), (f) obesity ($\text{BMI} > 35 \text{ kg/m}^2$; $n = 2$), and (g) more than 2 weeks of absence during the interventional period ($n = 3$). After detailed presentation of the study protocol, sixteen subjects were unwilling to join the randomization procedure and quit the study. Thus, finally 81 subjects were randomly assigned (computer generated block randomization ($n = 2-4$), stratified for age only) to two subgroups: (a) high intensity (interval) training (HI(I)T) group and (b) waiting-control group/moderate intensity continuous exercise (MICE) group, respectively, after crossover (Figures 1 and 4).

2.3. Measurements. Each participant was tested by the same researcher and at the same time of day (± 1 h). All assessments were determined in a blinded fashion. Researchers were not allowed to ask subjects about their exercise status (HIIT

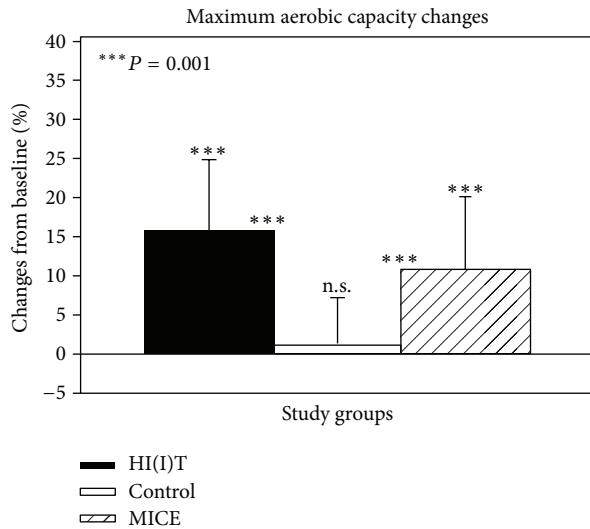


FIGURE 3: Percentage changes of relative VO₂ max in the RUSH study groups including the inactive CG. Asterisk (*) on the upper end of the error bar indicates significant changes within the group and asterisk between the bars indicates significant group differences. n.s. = nonsignificant.

or waiting CG/MICE). Each subject was provided with standardized rules for behaving prior to the tests in order to prevent confounding effects on primary and secondary endpoints (i.e., time to exhaustion (TTE) during stepwise treadmill test, blood pressure, and body composition).

2.3.1. Anthropometry. Height was determined with a stadiometer (Holtain, Crymych Dyfed, Great Britain). Weight, total, and regional body composition were determined using the bioimpedance technique (Inbody 230, Biospace, Seoul, Korea). Waist circumference was measured as the minimum circumference between the distal end of the rib cage and the top of the iliac crest along the midaxillary line.

2.3.2. Metabolic Syndrome Z-Score. MetS-Z-Score was calculated according to the formula proposed by Johnson et al. [25] based on the NCEP-ATP III criteria of the MetS [26]. According to these criteria five risk factors constituted the MetS: (1) raised triglyceride (TriGly) levels (≥ 150 mg/dL), (2) reduced HDL-C (< 40 mg/dL for males), (3) raised blood pressure ($\geq 130/85$ mmHG), (4) raised fasting plasma glucose (≥ 100 mg/dL), and (5) waist circumference (WC ≥ 102 cm for males).

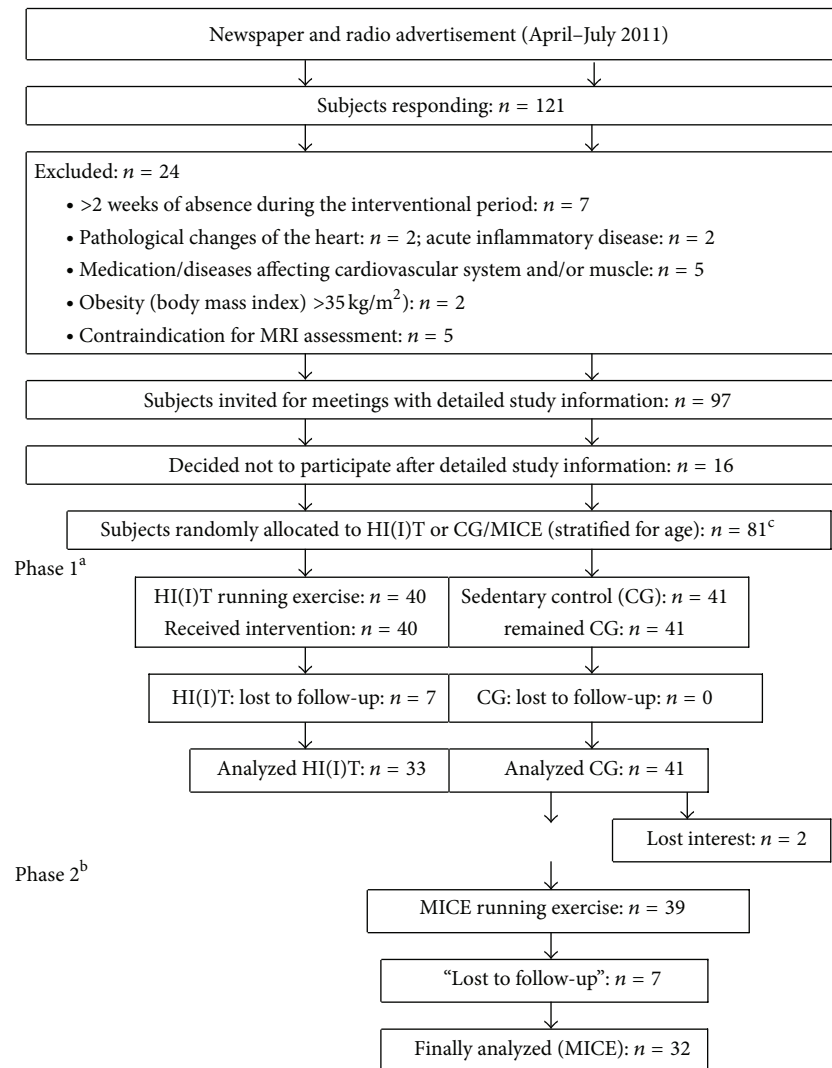
Following Johnson et al. [25], the ATP-III cut-point for a male population and the corresponding baseline standard deviation (SD) of the entire RUSH-cohort were used for each parameter (i.e., HDL-C and triglycerides) of the individual data. In detail, the Z-Score was calculated using $[(40 - \text{HDL-C})/\text{SD HDL-C}] + [(\text{TriGly} - 180)/\text{SD TriGly}] + [(\text{Glucose} - 100)/\text{SD Glucose}] + [(\text{WC} - 100)/\text{SD WC}] + [(\text{Mean arterial pressure (MAP)} - 100)/\text{SD MAP}]$.

2.3.3. Blood Parameters. Blood was sampled from an antecubital vein in the morning (7:00–9:00 a.m.) after a 12 h overnight fast. Serum samples were centrifuged at 3000 RPM for 20 min. Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, and uric acid (all: Olympus Diagnostica GmbH, Hamburg, Germany) were determined. During another visit, blood pressure was determined in a lying position after assessment of resting metabolic rate over 30 min, using an automatic oscillometric device (Bosco; Bosch, Jungingen, Germany). Subjects refrained from coffee and/or tea for at least 12 h before testing and with more than 12 h passing since the last relevant physical exertion or exercise session.

2.3.4. Aerobic Capacity (VO₂max) and Running Economy. During a stepwise treadmill test (3 min/1 km/h steps; 1° slope) up to a voluntary maximum, VO₂ was continuously determined breath by breath using an Oxycon mobile open spirometric system (Viasys, Conshohocken, PA, USA). For more details the reader is kindly referred to another publication [27]. Energy consumption/total work calculation according to the American College of Sports Medicine Guideline [28] is based also on VO₂ and RER-assessment considering the individual aerobic threshold.

Running economy (RE) was assessed for the last 30 sec of the second stage of the test (5:30 to 6:00 min), which was consistently kept below the anaerobic threshold [29].

2.4. Study Intervention. Figure 1 shows the design of the study intervention. For a detailed description of the intervention program the reader is referred to another publication [27]. Briefly, participants of the HI(I)T exercise group started on 16-week high intensity (running) exercise training in September 2011. After a short break around Christmas, participants of former control/waiting group started their 16-week moderate intensity continuous endurance exercise training in January 2012 and exercised until May 2012 (Figure 1). Each subject was provided with an individual training log that prescribed the intensity, volume, and frequency of the running exercise for the following 4 weeks. In both exercise groups, the weekly frequency of running exercise was progressively increased from 2 sessions/week at baseline to 3–4 sessions/week after week 8. With respect to exercise intensity the exercise protocols were based on individual prescriptions of the heart rate (HR) in different metabolic areas which were determined by stepwise treadmill test to a voluntary maximum and calculated based on the individual aerobic threshold concept (IAT: minimum lactate ~ 2.0 mmol/L) suggested by Dickhuth et al. [30]. The “Schwelle” Software (Schwelle Version 3, Bayreuth, Germany) was used to properly determine the IAT and the IAT-HR. In addition, the validity of the calculated IAT-HR was tested at baseline and after 8 weeks by running 30 min at this specification. Based on the subjects’ perceived exertion (“too high/too low”) IAT-HR was readjusted. In order to generate isocaloric condition and a comparable work load (in kcal) in both groups, running duration per exercise session was prescribed longer in the MICE group (57 ± 9 versus $53 \pm$



^aSeptember 2011 to December 2012 (Figure 1)

^bJanuary 2012 to May 2012 (Figure 1)

^cHI(I)T: high intensity (interval) training; MICE: moderate intensity continuous exercise

FIGURE 4: Flow chart of the RUSH study.

9 min/session) in order to compensate the higher intensity of the HI(I)T group [28].

Two sessions per week were consequently supervised by instructors who randomly checked exercise intensity by monitoring the HR watches (Polar RS 300, Kempele, Finland) which were provided for each participant.

2.4.1. HI(I)T Protocol. Figure 2 shows the rate of exercise volume in different metabolic areas for the HI(I)T and the MICE protocol. Briefly (core) exercise intensity during the intervention varied around 95%–110% of the IAT-HR (i.e., >85 to 97.5% HR_{max}) depending on the length of the interval (90 sec–12 min). Active rest periods of jogging or fast walking (1–3 min at 70–75% IAT-HR, ≈65–70% HR_{max}) were

prescribed between the intervals. Besides these intervals, continuous high intensity running sessions ranging from 25 to 45 min directly performed at the IAT (≈85% HR_{max}) were also part of the HI(I)T program. However 25% of total exercise volume of the HIIT group was performed at low exercise intensities (70–82.5% IAT-HR) during warm-up, cool-down, and the active rest periods (Figure 2).

2.4.2. MICE Protocol. With slight exceptions (IAT-HR tests), exercise intensity of the MICE intervention was prescribed consistently low to moderate (70–82.5% IAT-HR) (Figure 2). Duration of (continuous) running exercise was progressively increased during the 16 weeks of intervention and ranged from 35 to 90 min per session.

2.5. Statistical Procedures. The sample size calculation was based on another study endpoint (“left ventricular end-diastolic volume”) that is not presented here. Based on the sample size of 40 subjects per group and a Type 1 error of 5%, the statistical power ($1 - \beta$) to detect a $5 \pm 7.5\%$ difference between the groups was 85%. All the subjects who took part in the follow-up measurements were included in the analysis (“finisher analysis”).

Baseline and follow-up data are reported as mean values and standard deviations. Changes between baseline and follow-up in HI(I)T and MICE were reported as absolute (Table 2) and percentage changes (text, Figure 3). In addition, mean differences (with 95% confidence intervals) between HI(I)T and MICE based on absolute changes are reported (Table 2). Differences of baseline characteristics were checked by one-way Anova. Distribution of the data was statistically and graphically checked. Nonnormally distributed parameters were log-transformed to obtain normally distributed data. Differences within groups were consistently analyzed by paired *t*-tests. Analyses of variance with repeated measurements consequently adjusted for baseline values were performed to check time group interactions. With respect to the comparison of all groups, post-hoc “Scheffé test” was also calculated (Figure 3). All tests were 2-tailed; statistical significance was accepted at $P < .05$. Effect sizes (ES) were calculated using Cohen’s *d*. All statistical procedures were calculated with SPSS 21.0 (SPSS Inc., Chicago, IL) statistical procedures.

3. Results

Seven subjects of the HI(I)T (17.5%) and nine subjects of the MICE group were lost to follow-up (21%), while all the subjects of the CG ($n = 41$) were assessed. In this context, three subjects of the HI(I)T and four subjects of the MICE group quit the study due to injuries related to running exercise. One participant per group withdrew due to injuries related to the training protocol, two subjects of the HI(I)T and one subject of the MICE group due to injuries or diseases unrelated to exercise. Three subjects of the MICE and one subject of the HI(I)T group lost interest and cancelled their participation or did not start MICE after the control phase ($n = 2$).

Due to the comparable attendance rate of the HI(I)T (40.5 ± 5.4 sessions; $82.6 \pm 11.1\%$) and MICE group (40.3 ± 5.9 sessions; $82.3 \pm 12.0\%$) and the approach to compensate the higher exercise intensity of the HI(I)T group by higher exercise volume applied among the MICE group (2303 ± 352 min versus HI(I)T: 2092 ± 298 min; $P = .012$), total work was comparable between both groups (MICE: 30479 ± 6566 versus HI(I)T: 28966 ± 5228 kcal, $P = .317$).

Table 1 gives baseline characteristics of the subjects. With respect to these and other confounding factors (i.e., diet, lifestyle, exercise, medications, or diseases) that may have impacted the present results, no relevant differences at baseline (Table 1) or changes from baseline to follow-up were observed during study phase 1 or 2 (see Figure 4).

Weight significantly decreased in both exercise groups (HI(I)T: -1.3 ± 2.3 kg, $P = .004$ versus MICE: -2.5 ± 2.4 kg, $P = .001$); however, the reduction was significantly higher ($P = .046$) among the MICE participants. Significant weight gain (1.2 ± 2.3 kg, $P = .002$), resulting in significant differences ($P = .001$) compared to MICE and HI(I)T, was observed for the CG. Lean body mass was maintained in the HI(I)T- ($0.4 \pm 2.1\%$, $P = 0.381$) and CG ($0.7 \pm 2.3\%$; $P = 0.072$) but significantly dropped in the MICE group ($-1.1 \pm 1.8\%$, $P = 0.003$). Body fat mass similarly ($P = .261$) decreased in both exercise groups (HI(I)T: $-4.9 \pm 9.0\%$, $P = 0.010$ versus MICE: $-9.5 \pm 10.4\%$, $P < 0.001$) but increased in the CG ($3.4 \pm 9.1\%$, $P = .012$).

3.1. Study Endpoints. At baseline MetS-Z-Score and number of MetS parameters of the HI(I)T group were significantly higher compared with MICE and control (Table 2).

Metabolic Syndrome score according to Johnson et al. [25] significantly improved ($P = .001$) in both exercise groups (HI(I)T: -2.06 ± 1.31 versus MICE: -1.60 ± 1.77). Although changes of the control group were also significant (-0.30 ± 0.75 , $P = .042$) changes of both exercise groups were significantly more favorable ($P = .001$) (Table 2). At the same time, the number of MetS risk factors declined significantly ($P = .001$) in both exercise groups (HI(I)T: $21.9 \pm 25.6\%$ versus MICE: $43.8 \pm 31.5\%$; $P = .336$) and was unchanged in the CG (1.3 ± 25.6 , $P = 0.729$). Changes of both exercise groups for this parameter significantly differed ($P = .001$) from the CG ($3.5 \pm 17.9\%$, $P = .432$).

Thus the primary hypothesis that HIIT is significantly more effective compared with MICE to impact the Metabolic Syndrome (MetS) Z-Score and the number of criteria of the MetS clearly has to be rejected.

With respect to underlying mechanisms, Table 2 shows changes of parameters that constituted the MetS according to the NCEP ATP III MetS definition. Waist circumference was significantly reduced in both exercise groups (HI(I)T: $-2.3 \pm 2.7\%$ versus MICE: -2.6 ± 2.9 ; $P = .720$), while a nonsignificant rise ($P = .083$) was observed for the CG ($0.6 \pm 2.3\%$; $P = .001$ compared with both exercise groups). At the same time, significant reductions of MAP ($P = .001$) were observed for both exercise groups (HI(I)T: $-4.9 \pm 4.0\%$ versus MICE: -5.9 ± 4.2 ; $P = .318$) that significantly differed from the result of the CG ($0.3 \pm 4.4\%$; $P = .611$).

After adjusting for baseline values, no intergroup differences were determined for triglycerides that declined in all groups (HI(I)T: $-19.7 \pm 24.8\%$, $P = .001$ versus MICE: $-4.6 \pm 28.8\%$, $P = .361$ versus CG: $-6.8 \pm 33.9\%$, $P = .208$). HDL-C also changed favorably and reached significance level for all groups (HI(I)T: $8.8 \pm 5.3\%$, $P = .001$ versus MICE: $2.3 \pm 4.8\%$, $P = .014$ versus CG: $2.9 \pm 4.3\%$, $P = .001$). However, changes between the HI(I)T and the MICE as well as between HI(I)T and CG were significant ($P = .001$), while no difference was observed between MICE and CG ($P = .912$). Furthermore, no group (HI(I)T: $-1.4 \pm 10.0\%$ versus MICE: $-0.8 \pm 6.6\%$ versus CG: $-3.5 \pm 16.7\%$) showed significant changes ($P < .212$) of fasting glucose. Lastly, no between group differences were determined for this parameter ($P < .637$).

TABLE 1: Baseline characteristics of the RUSH study groups. No significant differences between the groups were determined.

Variables	HI(I)T group	MICE group	CG
Age (years)	43.9 ± 5.0	42.9 ± 5.1	42.5 ± 5.6
Body height (centimeter)	181.1 ± 7.0	181.6 ± 5.3	181.7 ± 5.3
Body weight (kilogram)	91.5 ± 14.0	89.5 ± 12.3	89.8 ± 15.5
Overweight (BMI > 25.0 kg/m ²) (n)	78%	73%	77%
Fat mass (%) ^a	25.5 ± 5.7	23.8 ± 6.0	23.9 ± 6.1
Physical activity (index) ^b	2.8 ± 1.4	2.6 ± 1.1	2.6 ± 1.1
Occupational working time (hours/week)	42.7 ± 8.5	44.8 ± 5.4	44.6 ± 7.4
VO ₂ max (mL/min/kg ⁻¹)	35.9 ± 5.6	39.5 ± 5.5	37.9 ± 6.3
Total exercise volume (minutes/week)	28.8 ± 32.1	32.4 ± 37.3	32.6 ± 37.5
“Athletic” history (n) ^c	31	29	29
Energy intake (kilocalorie/day)	2595 ± 738	2737 ± 592	2580 ± 616
Fat/protein/carbohydrates (gram/day)	96/104/305	105/105/322	96/104/297

^aAs assessed by bioimpedance analysis; ^bbased on a scale from 1 (very low) to 7 (very high) according to a subjective assessment of professional, household, and recreational activities; ^cformerly (13 ± 5 years ago) engaged in competitive sports with relevant demands on aerobic capacity (running, swimming, biking, triathlon, soccer, handball, and hockey); BMI: body mass index.

(Relative) VO₂max (mL·min⁻¹·kg⁻¹) significantly ($P = .001$) increased in both exercise groups (HI(I)T: $15.6 \pm 9.3\%$ versus MICE: $10.6 \pm 9.6\%$) with no significant difference between HIIT and MICE ($P = .121$). Relative VO₂max did not relevantly change in the CG ($1.1 \pm 6.4\%$, $P = .263$), thus, changes of both exercise groups significantly differed ($P = .001$) from the control. Of interest, nonweight adjusted absolute VO₂max (mL/min⁻¹) differed significantly ($P = .002$) between both exercise groups in favor of HIIT ($14.7 \pm 9.3\%$, $P = .001$ versus MICE: $7.9 \pm 7.4\%$, $P = .001$); however due to the significantly more distinct reductions of weight (but not LBM) in MICE this finding disappeared after calculating relative VO₂max changes (Figure 3).

Although these results make it difficult to generate a clear statement, for reasons discussed below, we also reject the secondary hypothesis that HIIT was significantly more effective to increase “cardiorespiratory fitness” compared with MICE.

4. Discussion

Summarizing the results, this study failed to detect a superiority of a HI(I)T compared with a MICE protocol on the Metabolic Syndrome (MetS) as a sensitive cluster of metabolic and cardiac risk factors even under the premise of comparable total “work” (...or “total energy consumption”) in both protocols (Table 2). However, compared with a nontraining control group both exercise protocols were highly effective for impacting the MetS, albeit by different mechanisms. While both protocols were similarly effective in reducing blood pressure and waist circumference, the effect of HIIT on blood lipids/lipoproteins was considerably higher compared with MICE. Three studies that either compared a high intensity interval [9, 21] or a high intensity continuous exercise protocol [25] with a MICE protocol while adjusting for energy consumption focused on the MetS cluster. In their pilot study with 22 subjects (52 ± 4 yr.) suffering from MetS

according to WHO [31], Tjønnå et al. [13] compared a HIIT (4×4 min at 90–95% HRmax intermitted by 3 min of active rest at 70% HRmax) with a traditional continuous running exercise training (47 min at 70% HRmax) performed 3 times per week. After 16 weeks of exercise the HIIT subgroup showed a significantly more pronounced reduction of the number of subjects with MetS (HIIT: -46% , $P < .05$ versus MICE: -37% ($P = .13$) and the number of MetS criteria (-32% , $P < .001$ versus 12% , $P < .05$) compared with MICE. However, applying continuous running exercise over 6 months for overweight subjects with “mild-to-moderate dyslipidemia” ($n = 86$, 40–65 yr.) Johnson et al. [25] did not confirm this superiority of high intensity exercise (65–80% VO₂peak; 128 min or 19 km/week) compared with MICE (40–55% VO₂peak; 205 min or 19 km/week). In contrast, although nonsignificant, the authors reported more favorable changes of MetS-Z-Score and number of MetS criteria according to NCEP-ATP III among the MICE subgroup. However, with respect to the general effectiveness of these exercise protocols on MetS parameters, both MICE and HI(I)T significantly outperformed the corresponding control group(s). Earnest et al. [9] generally confirmed the data of Johnson et al. [25] in their comparative exercise trial with 42 overweighted 32–60-year-old males. After 6 weeks of exercise ($3-4 \times \approx 40$ min/week with 50–70% VO₂max) subjects were randomly allocated to further 6 weeks of continuous running exercise at 50–70% VO₂max or a HIIT-protocol including up to 8 cycles of 2 min at 90–95% VO₂max intermitted by 2 min of active recovery (50% VO₂max). MetS-Z-Score according to the American Heart Association [32] and the number of MetS-risk factors (HIIT: -1.14 ± 1.15 versus MICE: -1.03 ± 1.68) significantly improved in both groups similarly. However, in a subgroup of persons at lower risk for insulin resistance (i.e., low HOMA-IR) only HIIT showed significant results. With respect to aerobic capacity/endurance performance both groups similarly and significantly improved (MICE: 3.1 versus HIIT: $2.9 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ or 2.8 versus 3.1 min during treadmill test). Of relevance, since body mass

TABLE 2: Effects of high intensity (interval) training (HI(I)T) versus moderate intensity continuous exercise (MICE) on Metabolic Syndrome parameters. Intergroup differences were adjusted for baseline values.

	HI(I)T ^a	MICE ^a	Mean difference 95% CI	P	ES ^b (d)
Metabolic Syndrome index (Z-Score)					
Before	0.95 ± 3.36	-1.82 ± 2.53	—	.001	
After	-1.11 ± 3.46	-3.42 ± 2.88	—	—	
Difference	-2.06 ± 1.31 ^{***a}	-1.60 ± 1.77 ^{***a}	0.46 (1.07 to -0.22)	.291	0.29
Numbers of risk factors of the Metabolic Syndrome (<i>n</i> out of 5)					
Before	2.51 ± 1.29	1.60 ± 1.13	—	.005	
After	1.97 ± 1.20	0.90 ± 1.09	—	—	
Difference	-0.55 ± 0.62 ^{***}	-0.70 ± 0.59 ^{***}	0.15 (-0.16 to 0.46)	.336	0.25
Waist circumference (cm)					
Before	101.5 ± 9.0	98.0 ± 9.5	—	.129	
After	99.2 ± 9.2	95.4 ± 9.3	—	—	
Difference	-2.3 ± 2.8 ^{***}	-2.6 ± 3.0 ^{***}	0.26 (-1.18 to 1.70)	.720	0.10
Mean arterial pressure (MAP) (mm/Hg)					
Before	111.5 ± 10.1	104.7 ± 7.1	—	.003	
After	106.6 ± 8.9	98.8 ± 7.2	—	—	
Difference	-4.9 ± 4.0 ^{***}	-5.9 ± 4.2 ^{***}	1.03 (-1.01 to 3.06)	.318	0.24
Triglycerides (mg/dL)					
Before	166.3 ± 85.1	127.0 ± 55.2	—	.013	
After	146.5 ± 82.2	122.4 ± 59.4	—	—	
Difference	-19.7 ± 26.8 ^{***}	-4.6 ± 28.8 ^{n.s.}	15.1 (2.0 to 28.2)	.083	0.54
High density lipoprotein Cholesterol (mg/dL)					
Before	43.1 ± 12.1	50.4 ± 10.7	—	.001	
After	51.9 ± 12.7	52.7 ± 10.4	—	—	
Difference	8.8 ± 5.3 ^{***}	2.3 ± 4.8 [*]	6.46 (3.88 to 9.05)	.001	1.29
Glucose (mg/dL)					
Before	92.2 ± 11.3	89.6 ± 8.3	—	.258	
After	90.7 ± 7.6	88.8 ± 8.8	—	—	
Difference	-1.5 ± 10.0 ^{n.s.}	-0.8 ± 6.6 ^{n.s.}	0.76 (5.18 to -3.46)	.693	0.008

^a Asterisk (*) indicate changes within the group (**P* < .05; ***P* < .01; ****P* < .001).

^b ES: effect size; 0.2: small; 0.5: moderate; 0.8: large.

decreased in both groups (-1.3 versus -2.3 kg), absolute VO₂max per se was not significantly affected (0.25 versus 0.13 L·min⁻¹) by the running protocols.

Revisiting the issue of whether some cardiometabolic MetS parameters are more sensitive to HIIT or to MICE, one might think that the large number of comparative trials, reviews, and meta-analysis that focus on this topic (e.g., [17, 33–37]) should allow a meaningful conclusion. However, in view of the large variety of confounders in these studies (e.g., sex, age, initial levels, health and fitness status, prescribed medication, and type of exercise) that may impact the effects of exercise on cardiometabolic risk factors, it is difficult to draw general conclusions. Also problematic for an adequate interpretation, most dose-response or comparative studies compared continuous (not interval) high intensity endurance

protocols that did not reach intensities (far) above the aerobic threshold [38]. Some of these studies that classified “moderate” or “vigorous” intensity at the lower end of the ACSM classification [33] (i.e., 3–6 MetS for moderate and 6–8 for vigorous exercise intensity) prescribed “high intensity workouts” that hardly exceed the exercise intensity of the MICE group in this study [36]. Taking these limitations into account and simply summarizing the data of present comparative studies, we are unable to detect a consistent superiority of HIIT versus MICE protocols (or vice versa) on cardiometabolic risk factors related to the MetS, independent of health, overweight, and fitness status [9, 13, 17, 22, 23, 39–42], although there are indeed some studies that reported more positive effects on single MetS risk factors for MICE or HIIT (e.g., [23, 24, 43]).

With respect to “cardiorespiratory fitness”, a strong tendency for higher VO_2max changes generated by the HIIT protocol of the present study was observed, which is mainly confirmed by comparative trials with untrained subjects with MetS or CHD/CVD [16, 17, 19, 20]. However, it is debatable whether higher VO_2max changes actually represented higher changes of cardiorespiratory fitness. In fact, this and other studies (e.g., [9]) observed even slightly higher changes of endurance performance (speed_{max}, time to exhaustion) by their MICE protocols, although VO_2max changes may be more distinct in the HI(I)T group. At first sight this result may appear contradictory, since VO_2max is an important predictor of endurance capacity [44]. However, it is not the only determinant of this complex topic [45, 46]. In fact, changes of running economy, another central determinant of endurance capacity, were significantly higher in our MICE group, which may account for the similar changes of endurance capacity. Thus, generating a comparable effect on endurance performance per se (i.e., TTE) the mechanism of HIIT versus MICE widely differs with respect to maximization (VO_2max) and economization (RE). Hence, although we think that VO_2max may in general be a valid characteristic for cardiorespiratory fitness, a conclusion whether or not HIIT protocols are superior for impacting cardiorespiratory fitness should not be based solely on this parameter.

Some limitations and features of the RUSH study may complicate a direct comparison with most HIIT protocols cited above: (1) due to the study protocol the exercise groups were not evaluated in parallel but consecutively (Figure 1). Thus, seasonable changes of physical activity or diet may have impacted our results, although no corresponding changes were detected by the follow-up questionnaires. (2) The study protocol prescribed a combination of HIT and HI(I)T with intervals of 90 sec to 12 min but also continuous bouts (25–40 min) at the IAT. Although around or above the aerobic threshold, this approach differs from purebred “HI(I)T” protocols defined as repeated very short (<45 sec) or short (2–4 min) bouts of high to near maximum intensity exercise [47]. (3) Although on the majority overweight, only in 33% of the RUSH participants the MetS was prevalent. Correspondingly, the average numbers of MetS criteria per subject were rather low (2.0 ± 1.2), which may prevent a more distinct reduction of this parameter. Therefore the authors opt for the use of the MetS-Z-Score, a continuous score that is based on individual subjects (raw) data, which may be more appropriate to properly assess the effect of the study intervention [25]. (4) The drop-out rates in both exercise groups were rather high ($\approx 20\%$). Independent of the exercise intensity, half of these subjects cited orthopedic problems for their withdrawal. Furthermore, a slight majority (HIIT: $n = 16$ versus MICE: $n = 15$) of the remaining males reported musculoskeletal problems and complaints longer than 7 days. These adverse effects may be related to the high body weight in this cohort and the abruptly increased mechanical impact due to the unaccustomed running exercise and the speedy progression of the running program. (5) With respect to exercise (intensity) compliance the authors did not analyze all the heart rate watches after the session but randomly selected 15–20 subjects per session (i.e., 50%) for this procedure.

(6) In order to adequately focus on the effect of exercise intensity, unlike most other studies with healthy untrained persons, comparable work load for both groups was prescribed. However, the authors are aware that time effectiveness is an important benefit of HIIT protocols that largely account for its attractiveness [48].

In summary, both protocols favorably impacted cardiometabolic risk factors; however the superiority of HIIT protocols for positively impacting MetS as a cluster of relevant metabolic and cardiac risk factors cannot be confirmed, at least for this cohort of untrained middle-aged males. Furthermore, although VO_2max changes were significantly higher in the HI(I)T group, based on the slightly higher MICE effect on endurance capacity, we do not share the enthusiasm of other researchers in recommending pure HIIT protocols for increasing “cardiorespiratory fitness”. We would rather favor a skilled combination of higher and lower exercise intensity (and volume) that may optimally affect performance parameters related to both economy and maximization.

5. Conclusion

Addressing the strengths and limitations of HIIT protocols in the field of primary and secondary prevention, time efficiency along with effectiveness is a clear pro for HIIT, taking into account the sedentary lifestyle and low affinity to exercise of most middle-aged subjects [7]. At the same time, there is some evidence that HIIT was perceived as “more enjoyable” compared with the more monotone MICE [49] another pro that may increase exercise adherence. One may argue that the rather high intensity of HIIT may provoke cardiovascular complications during exercise at least in subjects with cardiovascular diseases. However, although the statistical power of this study may be still (≈ 176.000 exercise training hours at all) too low to detect differences between groups, a recent study of Rognmo et al. [12] listed extremely low rates of CHD events for both methods HIIT and MICE.

Thus, although we cannot confirm the general superiority of HIIT, with respect to efficiency and adherence, we strongly recommend HIIT as a reasonable component of endurance exercise protocols for prevention and rehabilitation of cardiometabolic diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

High-Intensity Interval Training in Patients with Substance Use Disorder

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Patients with substance use disorder (SUD) suffer a higher risk of cardiovascular disease and other lifestyle diseases compared to the general population. High intensity training has been shown to effectively reduce this risk, and therefore we aimed to examine the feasibility and effect of such training in SUD patients in clinical treatment in the present study. 17 males and 7 females (32 ± 8 yr) in treatment were randomized to either a training group (TG), treadmill interval training in 4×4 minutes at 90–95% of maximal heart rate, 3 days a week for 8 weeks, or a conventional rehabilitation control group (CG). Baseline values for both groups combined at inclusion were 44 ± 8 (males) and 34 ± 9 (females) $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, respectively. 9/12 and 7/12 patients completed the TG and CG, respectively. Only the TG significantly improved ($15 \pm 7\%$) their maximal oxygen consumption ($\text{VO}_{2\text{max}}$), from $42.3 \pm 7.2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ at pretest to $48.7 \pm 9.2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ at posttest. No between-group differences were observed in work economy, and level of insomnia (ISI) or anxiety and depression (HAD), but a significant within-group improvement in depression was apparent for the TG. High intensity training was feasible for SUD patients in treatment. This training form should be implemented as a part of the rehabilitation since it, in contrast to the conventional treatment, represents a risk reduction for cardiovascular disease and premature death.

1. Introduction

Patients with substance use disorder (SUD), classified within ICD-10: F10-19 (mental and behavioral disorders due to psychoactive substance use) at the World Health Organization's mental and behavioral disorders classification, have a high prevalence of health and psychosocial problems in addition to their substance use disorder [1]. Although this patient group's disorder indeed has multifactorial causes, the evidence of how their physical capacity may be related to their calamitous lifestyle is sparse. Contributing to a decreased life expectancy of 15–20 years, the lowest among patients with different mental illnesses [2, 3] is an increased prevalence of cardiovascular disease [4–6]. The high risk of developing cardiovascular disease is associated with the population's drug use, poor nutrition, and obesity but is also likely a direct result of the patient group's inactivity [3].

Endurance training, especially with emphasis on high intensity, is shown to increase aerobic power and reduce the risk of cardiovascular disease [7–10]. Improvements of 10–30% in maximal oxygen consumption ($\text{VO}_{2\text{max}}$) have typically been observed in these studies, after training interventions of 2–3 months. These improvements may also be associated with large reductions in the risk of mortality, as an improvement of 1MET ($\sim 3.5 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) is shown to reduce the mortality rate by 12% [11]. Adding to the physical benefits of exercise are also possible effects on mental health. Although little is known about the effects of high-intensity interval training in SUD patients, exercise has been documented to have an overall beneficial effect on mental health and quality of life in patients with mental illnesses [12].

Despite the well-documented effect on cardiovascular disease risk reduction [7, 8, 10], decreased mortality rate [11, 13, 14], and improved mental health [15–19], effective

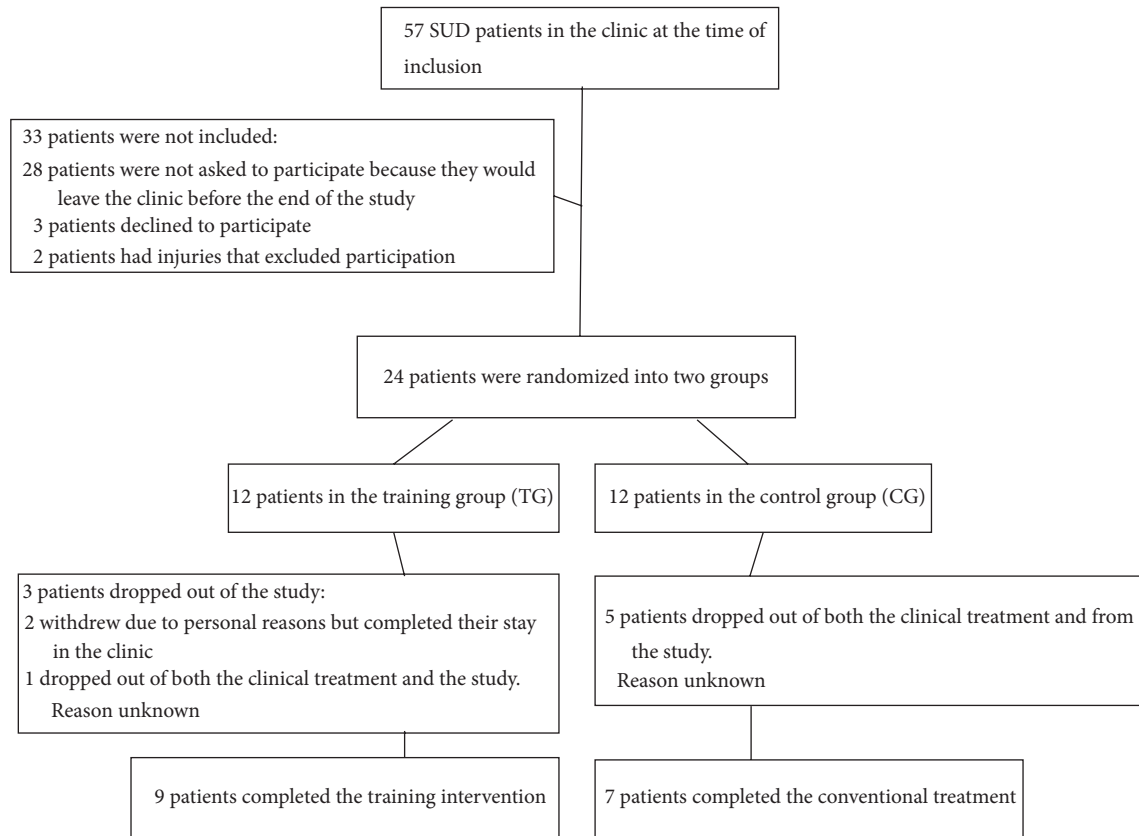


FIGURE 1: Recruitment, randomization, and withdrawal of SUD patients throughout the study.

physical training appears not to be a part of the conventional treatment for SUD patients. There has certainly been physical activities in the clinics for more than 30 years [20], but in general this activity seems random and unstructured and the frequency and intensity of the activities are often unknown. Indeed the activities may vary between clinics, but to our knowledge, it has not been documented that whole body exercise with a high intensity ($\geq 85\%$ of HR_{max}) constitutes a part of the clinical program. As physiological parameters rarely are documented, knowledge of physical status or improvements remains uncertain. Therefore, the aim of the present study was to examine if high-intensity interval training was feasible for SUD patients in treatment. Further, we aimed to document their aerobic power and compare the training group, if they were able to adhere, with patients receiving conventional treatment in the same clinic. Our hypotheses were that SUD patients (1) are able to complete a high-intensity interval training program, (2) have a decreased aerobic power at baseline compared to the average population, and (3) improve their VO_{2max} and work economy more than the control group receiving conventional rehabilitation.

2. Methods

2.1. Subjects. 24 patients with a diagnosis of substance use disorder, ICD-10: F10-F19, were included in this study. All subjects participated in residential long term treatment in a

substance abuse treatment clinic at the time of the study, due to abuse of illegal drugs. The long term treatment program at the clinic lasts for ~ 3 months. Subjects were excluded if they had been abstinent or/and systematically participated in endurance training for the last six months. Subjects were also excluded if they had cardiovascular disease or chronic obstructive pulmonary disease or were not able to perform treadmill testing and training. After signing the written informed consent, patients were randomized to either a high intensity training group (TG) or a conventional rehabilitation control group (CG) (Figure 1). Patient characteristics and medical use are given in Table 1. The regional ethical committee did approve the study, and it was carried out in accordance with the Declaration of Helsinki.

2.2. Testing

2.2.1. Maximal Oxygen Consumption and Work Economy. Measurements of VO_{2max} , work economy, and ventilatory parameters were obtained using the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany), walking/running on a treadmill (Woodway Weil am Rhein, Germany). After a 10-minute warm-up period, the subjects walked at $4.5 \text{ km} \cdot \text{h}^{-1}$ at 5% inclination for a period of 5 minutes. The average oxygen consumption for the last minute of this period was recorded as the work economy. Immediately following the work economy test, the

TABLE 1: Patient characteristics and medical use.

	TG (n = 9)	CG (n = 7)	Combined (n = 16)
Men/women (n)	8/1	5/2	13/3
Age (yr)	33 ± 11	31 ± 8	32 ± 9
Height (cm)	177 ± 10	175 ± 10	176 ± 10
Weight (kg)	84.1 ± 14.9	87.9 ± 20.8	85.8 ± 17.2
Current smoker	8	6	14
Drug use debut (age)	15 ± 6	17 ± 4	16 ± 5
Duration of abuse (yr)	17 ± 8	12 ± 4	15 ± 7
Primary drug			
Heroin	1	1	2
BZD, Sed, Hypn	1	1	2
Amphetamine	4	4	8
Cannabis	3	1	4
Secondary drug			
Alcohol	2	0	2
Heroin	1	1	2
Opiates, painkillers	2	1	3
Amphetamine	1	0	1
Cannabis	3	5	8
Symptoms for medicine prescription:			
ADHD	0	1	1
Allergies	1	2	3
Anxiety	2	1	3
Arthritis	0	1	1
Asthma/COPD	0	1	1
Depression	1	2	3
Epilepsy	0	1	1
Hypertension	3	1	4
Schizophrenia/bipolar	1	2	3
Substitutional treatment	1	1	2
Other	0	3	3

Data are presented as mean ± SD; TG: training group; CG: control group, Type of medication is reported on indication of symptoms according to common directory. The prescribed medicines in substitutional treatment are methadone and suboxone. Others: skin disorder, pain, and inflammation.

subjects continued to the $VO_{2\max}$ test. The incline was kept at 5% while velocity was increased by $1 \text{ km} \cdot \text{h}^{-1}$ every minute until exhaustion. $VO_{2\max}$, respiratory exchange ratio (RER) and ventilation were calculated averaging the three highest continuous 10 second values. One or more of the following criteria for reaching $VO_{2\max}$ were considered [21]: (1) if the oxygen consumption reached a plateau despite further increases in workload, (2) a RER above 1.05, and (3) lactate concentration in blood ($[\text{La}^-]_b$) > 7 mmol. Maximal heart rate (HR_{\max}) was calculated as 4 beats $\cdot \text{min}^{-1}$ added to the highest heart rate during the last minute [22]. For heart rate assessment Polar F6 heart rate monitors were used (Polar Electro, Finland). $[\text{La}^-]_b$ were measured using the Biosen C-line (EKF Diagnostics GmbH, Barleben, Germany)

analyzer. Blood from the patient's fingertip was sampled for analysis of blood lactate within 1 min after the $VO_{2\max}$ test. As an expression of maximal aerobic power, inclination and velocity at $VO_{2\max}$ were registered.

2.2.2. Identification of Drug Use. For identification of the extent of drug use the first page of EuropASI was applied (Addiction Severity Index, European adaption of The American 5th edition [23]). This index quantifies which substances have been used, when the patients started their use, and for how long the dependency has lasted. Further, the medical use for the patients participating in the study is given in Table 1.

2.2.3. Insomnia, Anxiety, and Depression Questionnaires. In addition to the physical testing two questionnaires were implemented; Insomnia Severity Index (ISI) to detect possible cases of insomnia and Hospital Anxiety and Depression Scale (HAD) which is used to estimate the levels of anxiety and depression. These self-report questionnaires were answered before and after the training intervention as measures of psychological changes during the period of the study. The ISI has been evaluated to be a clinically useful tool for screening and quantifying perceived insomnia severity [24]. It is composed of 7 items targeting different categories of sleep disturbance severity. The items are rated at a five-point Likert scale (0–4) summed up to a total score ranging from 0 to 28, where a higher score indicates more severe insomnia. The score categories are 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe). The HAD self-assessment scale is consisting of a fourteen item scale, seven items related to anxiety and seven related to depression. On the subscales for anxiety and depression a score of 0–7 for either subscale is estimated within the normal range, while a score of 11 or higher implies a probable presence of a mood disorder. A score of 8–10 is considered signs of a mood disorder [25].

2.3. Training Intervention. Both the TG and the CG participated in the clinic treatment activities throughout the 8-week intervention period. These activities included: Ball-games (indoor-soccer and volleyball), yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games. Additionally, the TG received supervised training 3 times a week for a period of 8 weeks. The training was performed as inclined walking or running on a treadmill, using the same heart rate monitor as during the $VO_{2\max}$ testing, to ensure correct intensity of every training session. The training sessions were organized as interval training, with 4×4 minutes of high aerobic intensity (90–95% of HR_{\max}), interrupted by 3-minute recovery periods (~70% of HR_{\max}) [21]. All training sessions were supervised. As the subjects improved, velocity and incline were increased to meet the targeted heart rate. The subjects needed to have an adherence of at least 20 out of 24 training sessions in order to be included in the data analyses. Within the same time period as the TG performed their high-intensity interval training on a treadmill, the patients in the CG chose to participate

TABLE 2: Changes in physiological parameters from pre- to posttest.

	TG (N = 9)		CG (N = 7)	
	Pre	Post	Pre	Post
VO _{2max}				
(L·min ⁻¹)	3.60 ± 0.91	4.15 ± 1.03 ^{**#}	3.43 ± 0.66	3.54 ± 0.65
(mL·kg ⁻¹ ·min ⁻¹)	42.3 ± 7.2	48.7 ± 9.2 ^{**#}	41.8 ± 12.3	42.6 ± 12.1
V _E (L·min ⁻¹)	109.2 ± 28.6	125.9 ± 36.8 ^{**#}	103.5 ± 24.4	103.2 ± 23.9
RER	1.09 ± 0.03	1.10 ± 0.02	1.17 ± 0.11	1.14 ± 0.06
HR _{max} (beats·min ⁻¹)	180 ± 11	181 ± 14	189 ± 7	188 ± 7
[La ⁻] _b	9.12 ± 2.41	10.65 ± 1.69	8.04 ± 3.54	9.21 ± 2.01

Data are presented as mean ± SD. TG: training group; CG: control group; VO_{2max}: maximal oxygen uptake; V_E: ventilation; RER: respiratory exchange ratio; HR_{max}: maximal heart rate; [La⁻]_b: lactate concentration in blood, ^{**}*P* < 0.01, difference within group from pre- to posttest, [#]*P* < 0.05, differences in changes from pre- to posttest between groups.

in a self-elected activity among the offered sports or games in the clinical treatment program. Although representing a wide range of different activities, they all shared a measured or estimated intensity level of <70% of HR_{max}.

2.4. Statistics. Statistical analyses were performed using the software SPSS, version 20 (Chicago, USA), and figures were made using the software GraphPad Prism 5 (San Diego, USA). Relative improvements are given as mean percentage change. To determine if the data was normal distributed a Q-Q plot was used. Repeated measures ANOVAs (2 (group) × 2 training status) were used to determine differences between groups following training. If appropriate, a Tukey post hoc analysis was used. Unpaired and paired *t*-tests were used to detect differences between groups at baseline and within group following training, respectively. Statistical significance was accepted at an α -level of *P* < 0.05. Data are reported as mean ± SD, unless otherwise noted. Additionally, using similar statistics, an intention to treat analysis with the use of last observation carried forward for missing data was carried out for all the 24 subjects that were randomized to the two groups. To achieve a statistical power of 80%, 8 patients in each group needed to complete the study period in order to observe a 0.375 L · min⁻¹ improvement difference in mean VO_{2max} between TG and CG, assuming a SD of 0.25 L·min⁻¹. These values were based on previous studies from our group using the same training intervention in other populations. The drop-out rate in previous studies has been ~2/10 subjects. However, considering that this patient population may be more challenging than average, a higher drop-out rate is expected. Thus 12 subjects were randomized to each group to ensure observation of the assumed efficacy difference between the two groups.

3. Results

11 of the 12 SUD patients in the TG and 7 out of 12 patients in the CG, respectively, completed their overall intended stay at the substance use disorder clinic. With regard to the high intensity training, 3 subjects withdrew from the TG. Two withdrew due to personal reasons but remained in the clinical treatment, while one dropped out from both the clinical

treatment and the TG. In the CG 5 subjects dropped out of the clinical treatment and thus withdrew from the study without giving any reasons (Figure 1). The SUD patients that completed the training period carried out 22 ± 1 of the scheduled supervised training sessions. The targeted intensity (90–95% of HR_{max}) was reached in all completed sessions. None of the subjects reported any problems or discomfort completing the training sessions, other than the normal strain following high intensity exercise.

At baseline, before the withdrawal of subjects from the study, values for both groups combined were 44 ± 8 (males) and 34 ± 9 (females) mL · min⁻¹ · kg⁻¹, respectively. VO_{2max} significantly (*P* < 0.01) improved by 15 ± 7% for the 9 subjects that completed the TG (Table 2). This improvement was also significantly (*P* < 0.01) different from the CG (Figure 2). In accordance with the improvement in aerobic power, the TG also increased velocity and inclination at VO_{2max} from 9.2 ± 2.3 km · h⁻¹ and 5.6 ± 1.1% at pretest to 9.3 ± 2.2 km · h⁻¹ and 8.3 ± 2.4% at posttest. The CG showed no within-group improvement in neither VO_{2max} nor maximal workload. The TG increased ventilation at VO_{2max} by 14 ± 10%, while there were no differences within or between groups in RER or [La⁻]_b at VO_{2max} from pre- to posttest. An intention to treat analysis, including all 24 participants that were randomized to either the TG or the CG, did not show different results for the primary outcomes compared to analysis including only subjects that completed the study.

Work economy, measured at 5% inclination and 4.5 km · h⁻¹ on the treadmill, showed no significant differences between or within the two groups following the training period (Table 3). However, the heart rate at the work economy workload significantly (*P* < 0.05) decreased by 9 ± 12% in the TG, but this within-group change was only apparent as a trend (*P* = 0.158) when compared to the CG.

For psychological variables, the TG displayed a significant (*P* < 0.05) decrease in depression level following the training period, whereas the CG had a significant decrease (*P* < 0.05) in anxiety level from pre- to posttest (Table 4). However, neither of these within-group differences, measured by the Hospital Anxiety and Depression questionnaire, was apparent as between-group differences.

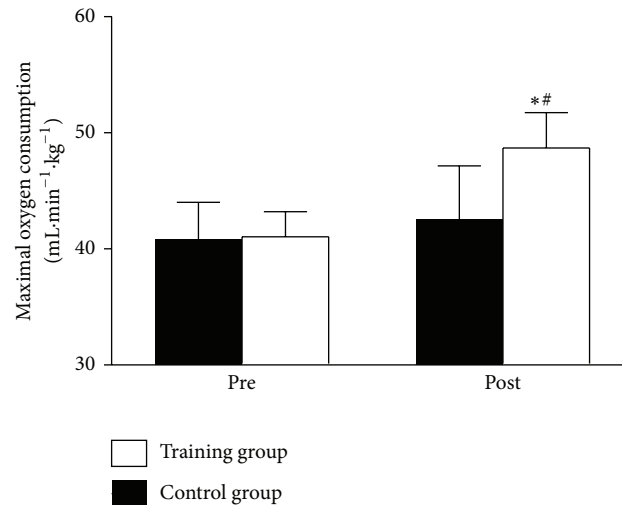


FIGURE 2: Maximal oxygen consumption before and after the training intervention. Data are presented as mean \pm SE. * $P < 0.01$, difference within group from pre- to posttest, # $P < 0.05$, differences in changes from pre- to posttest between groups.

TABLE 3: Work economy measured at 4.5 km·h⁻¹ and 5% inclination at pre- and posttest.

	TG (N = 9)		CG (N = 7)	
	Pre	Post	Pre	Post
VO ₂				
(L·min ⁻¹)	1.54 \pm 0.24	1.61 \pm 0.28	1.70 \pm 0.36	1.77 \pm 0.43
(ML·kg ⁻¹ ·min ⁻¹)	18.5 \pm 1.1	18.9 \pm 1.3	19.6 \pm 2.3	20.2 \pm 1.4
V _E (L·min ⁻¹)	35.1 \pm 4.4	33.3 \pm 5.3	38.3 \pm 9.3	41.1 \pm 9.0
RER	0.90 \pm 0.04	0.89 \pm 0.08	0.93 \pm 0.05	0.94 \pm 0.07
HR _{max} (beats·min ⁻¹)	116 \pm 17	105 \pm 18	116 \pm 18	119 \pm 9

Data are presented as mean \pm SD. TG: training group; CG: control group; VO₂: oxygen uptake; V_E: ventilation; RER: respiratory exchange ratio; HR_{max}: maximal heart rate.

TABLE 4: Psychological changes from pre- to posttest (scores from the insomnia severity index and hospital anxiety and depression scale questionnaires).

	TG (n = 9)		CG (n = 7)	
	Pre	Post	Pre	Post
Anxiety	9.4 \pm 3.5	8.6 \pm 2.5	9.1 \pm 5.3	6.3 \pm 3.4*
Depression	8.5 \pm 4.8	5.3 \pm 3.9*	6.0 \pm 3.5	4.6 \pm 3.5
Insomnia	10.6 \pm 5.4	8.9 \pm 5.1	10.9 \pm 10.1	9.1 \pm 5.0

Data are presented as means \pm SD. TG: training group; CG: control group. * $P < 0.05$, difference within group from pre- to posttest.

4. Discussion

Since little is known about the aerobic power of SUD patients in treatment and their lifestyle indicates that they may suffer a high risk of cardiovascular and lifestyle diseases, this study sought to investigate the aerobic power of this group of patients and their response to exercise training of high intensity. The main findings of the study were as follows (1) the initial aerobic power at baseline is lower than what is typically seen in the average population, (2) the SUD patients improved their aerobic power and work performance following the training intervention, thus decreasing the risk

factors for lifestyle diseases, and (3) the training intervention is applicable as a part of the clinical treatment.

4.1. Reduced Aerobic Power in Patients with Substance Use Disorder. At inclusion, the SUD patients in the present study had a baseline VO_{2max} of 44 \pm 8 (males) and 34 \pm 9 (females) mL · min⁻¹ · kg⁻¹. This is well below age-matched reference data from the average population [26]. The 10% and 16% lower baselines for the ~30 year old males and females, respectively, are comparable to the average values observed among 50–59-year-old healthy subjects [26]. The low aerobic power, as documented in the current study, is in line with a previous study displaying VO_{2max} values of 39 (males) and 31 mL · min⁻¹ · kg⁻¹ (females) in SUD patients [27]. Our study and the Mamen and Martinsen [27] study are to our knowledge the only studies to directly assess aerobic power in SUD patients. However, the assumption of a health-related critical low aerobic power is also supported by several studies applying estimations of VO_{2max} [17, 28–31]. Since low aerobic power is a well-established risk factor for cardiovascular disease and all-cause mortality [11, 13, 14, 32], it is likely that the low VO_{2max} observed among SUD patients may, at least in part, be responsible for the elevated prevalence of cardiovascular disease and premature death observed in this patient group.

It is therefore surprising that aerobic power commonly is not listed as one of the major causes for illnesses, medical conditions, and early death in SUD patients [3, 4, 6].

4.2. Exercise-Induced Effect on Aerobic Power, Work Load, and Risk Reduction. As expected, the SUD patients that completed the supervised eight week treadmill training period in the current study improved $\text{VO}_{2\text{max}}$. In accordance with the $15 \pm 7\%$ improvement in $\text{VO}_{2\text{max}}$, the TG increased maximal velocity and inclination at $\text{VO}_{2\text{max}}$ from $9.2 \pm 2.3 \text{ km} \cdot \text{h}^{-1}$ and $5.6 \pm 1.1\%$ at pretest to $9.3 \pm 2.2 \text{ km} \cdot \text{h}^{-1}$ and $8.3 \pm 2.4\%$ at posttest. For patient groups with low aerobic capacities, daily activities are often perceived as strenuous. An improvement in work capacity is therefore typically associated with an increased wellbeing in everyday life, since it reduces the relative intensity on the daily tasks [10, 33, 34]. The improvement in $\text{VO}_{2\text{max}}$ observed in our study is similar to what have previously been reported following a whole body high intensity ($>85\%$ of HR_{max}) training intervention in a wide range of patient groups [7–10, 35, 36], as well as and in healthy subjects [21, 37] and old subjects [37]. The magnitude of $\text{VO}_{2\text{max}}$ improvement may be influenced by training status, age, or pathology [7–10]. Subjects with a low baseline are, both mathematically and physiologically, susceptible to larger percentage improvements ($\sim 15\text{--}35\%$) than subjects with a higher baseline ($\sim 6\text{--}13\%$) [21, 37].

Considering the elevated risk of mortality [3] and cardiovascular incidents in SUD patients [4], $\text{VO}_{2\text{max}}$ improvements as demonstrated in the present study are beneficial. A $3.5 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ improvement in $\text{VO}_{2\text{max}}$ has been shown to be associated with a 12% improved chance of survival [11] and a 15% reduced risk for developing cardiovascular disease [32]. The SUD patients in the present study improved their $\text{VO}_{2\text{max}}$ by $6.6 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, indicating that not only will they have a strongly decreased mortality rate, but also a considerable reduced risk of developing cardiovascular disease. After the relatively short-duration training period the SUD patients restored their $\text{VO}_{2\text{max}}$ values to a level similar to the age-matched healthy population [26]. In contrast, it is thought provoking that conventional clinical treatment did not improve $\text{VO}_{2\text{max}}$. Physical activity is certainly applied in today's treatment [20], but clearly this physical activity is not sufficient to induce improvements in $\text{VO}_{2\text{max}}$. Since the conventional activities are all reported to be carried out with a low intensity, this may explain the lack of improvement, as intensity is suggested to be the key factor for $\text{VO}_{2\text{max}}$ improvements [21, 38]. Recognizing the high risk for cardiovascular disease and mortality in these patients, it is critical that today's treatment may have no effect on one of the most important factors for these conditions.

The exercise-induced improvement in $\text{VO}_{2\text{max}}$ that was observed in the TG is likely due to an improvement in maximal cardiac output, and more specific is the stroke volume of the heart since no changes were observed in HR_{max} . Previously the stroke volume has been shown to be the decisive factor that explains the adaptations to high intensity training, both in moderately trained healthy subjects [21]

and in untrained coronary artery disease patients [39]. The $\sim 42 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (males and females combined) baseline $\text{VO}_{2\text{max}}$ in the current study falls between an aerobic power of ~ 55 (young, healthy) and ~ 27 (coronary artery disease) $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. Although the SUD patients indeed represent a different group of subjects, it is likely, since the stroke volume adaptations appear to be similar across different populations, that also their improvements in $\text{VO}_{2\text{max}}$ originate from training-induced changes in maximal stroke volume.

4.3. Training Effect on Insomnia, Anxiety, and Depression. A positive relationship between exercise and mood disorders is well-documented [20, 40–44] specifically apparent as insomnia [40, 45], anxiety [44], and depression disorder [41, 43, 46] reductions. Therefore, it is surprising that the large difference between the TG and the CG in aerobic power and work load following the study period did not induce detectable differences between groups in any of these variables. At baseline, the level of mental distress in both the TG and the CG group was ranged as moderately severe according to the Insomnia Severity Index and the Hospital Anxiety and Depression Scale. Both groups scored within subthreshold for insomnia and within signs of mood disorder. Following the study period there was a reduction of the depression variable within the TG, as well as a reduction of the anxiety variable within the CG, but these reductions were not different between the two groups. It is possible that psychological benefits, as measured by the questionnaires in our study, are more related to physical activity per se and not necessarily to aerobic exercise training. Although reduced depression symptoms may be associated with exercise in general and not necessarily restricted to the aerobic form of exercise [15], it should undoubtedly be expected that a risk reduction of cardiovascular disease and mortality would cause an improvement of mood disorders and quality of life [42]. Thus the commonly applied questionnaires that were used in our study should be able to detect such an improvement. Our results indicate that a supplement, expansion, or replacement to/of the questionnaires are sought for, although it is recognized that the relatively small sample size in the current study may be, in part, responsible for the nondetectable differences in mood disorders.

4.4. High-Intensity Interval Training: Clinical Implications. Considering their high rate of nonattendance and discontinuation [47, 48], reflected in the high relapse rates from clinical treatment [49], an important question in the current study was whether the SUD patients were able to carry out the scheduled period of training. To our knowledge there have not been any previous reports of SUD patients participating in such an intensive training intervention. The SUD patients were in our study capable of managing the intensive training, reflected in the high attendance (22 ± 1 of the total 24 scheduled training sessions) for the 9 subjects that completed the training period. Interestingly, the completion rate was higher for the TG, both in the current study and in the clinical treatment, compared to the CG. Only 1 out of 12 patients in the TG dropped out from clinical treatment (5 subjects in the CG) and 3 from the training study (5 subjects in the

CG). Certainly these withdrawals could be due to chance, but the completion rate is nevertheless a testament to the feasibility of high-intensity interval training as part of the clinical treatment. An intention to treat analysis showed no differences in the main findings of the current study and thus strengthens the result of an overall beneficial effectiveness of high-intensity interval training in a clinical setting. Not only was it feasible to apply this intervention in the clinic, but additionally the subjects that completed the training reported no discomfort or pain during the training sessions other than what should be expected with high intensity training, and not one single commenced training session was aborted.

Our findings are in line with a previous study applying a similar training intervention in patients with schizophrenia [10]. In the Heggelund et al. study [10] the training was reported to be challenging but feasible. In our study, as well as in the Heggelund et al. study [10], all trainings were conducted in presence of a supervisor. This may be favorable when implementing a training intervention in mentally ill patients. Mamen et al. [50] emphasized that the relationship between the patient and the supervisor can prove essential for the patients motivation and commitment to the project. Our experience throughout this study supports this notion. The present study exemplifies that high intensity training can be applicable for SUD patients in treatment and that the intensive training is manageable also for this patient group. Considering the health benefits associated with this training, it should be implemented as a complementary treatment for SUD patients.

5. Conclusion

In the present study SUD patients are shown to have a low aerobic power, and thus they are at risk for developing cardiovascular disease. As it is important that SUD patients receive both a physical and psychological treatments in the clinic and our results indicate that the conventional treatment is not sufficient to reduce the risk of cardiovascular disease, high-intensity interval training should be implemented as part of the clinical treatment to effectively improve the patient groups' aerobic power.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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Research Article

The Effect of a Short-Term High-Intensity Circuit Training Program on Work Capacity, Body Composition, and Blood Profiles in Sedentary Obese Men: A Pilot Study

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The objective of this study was to determine how a high-intensity circuit-training (HICT) program affects key physiological health markers in sedentary obese men. Eight obese (body fat percentage > 26%) males completed a four-week HICT program, consisting of three 30-minute exercise sessions per week, for a total of 6 hours of exercise. Participants' heart rate (HR), blood pressure (BP), rating of perceived exertion, total work (TW), and time to completion were measured each exercise session, body composition was measured before and after HICT, and fasting blood samples were measured before throughout, and after HICT program. Blood sample measurements included total cholesterol, triacylglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and insulin. Data were analyzed by paired *t*-tests and one-way ANOVA with repeated measures. Statistical significance was set to $P < 0.05$. Data analyses revealed significant ($P < 0.05$) improvements in resting HR (16% decrease), systolic BP (5.5% decrease), TW (50.7%), fat tissue percentage (3.6%), lean muscle tissue percentage (2%), cholesterol (13%), triacylglycerol (37%), and insulin (18%) levels from before to after HICT program. Overall, sedentary obese males experienced a significant improvement in biochemical, physical, and body composition characteristics from a HICT program that was only 6 hours of the total exercise.

1. Introduction

Resistance training and aerobic exercise are established approaches to help manage obesity and associated risk factors [1–5]. Both types of exercise have been prescribed to sedentary and obese individuals, and resulted in improved blood pressure (BP), heart rate (HR), body composition, biochemical markers (insulin, glucose, cholesterol, etc.), and strength [6–15]. Combination training (i.e., aerobic and resistance training combined) appears to have a greater effect on BP, arterial stiffness, body composition, and $\text{VO}_{2\text{max}}$ than performing either type of exercise independently [13, 14]. Thus, combination training may be a more optimal mode of exercise prescription for the obese population.

One form of combination training is circuit training (CT) which incorporates both multijoint resistance training and callisthenic exercises that keeps the heart rate elevated for the duration of the training session [16]. During CT an individual moves from exercise to exercise as quickly as possible with very little rest, which results in a short duration exercise session. The rest intervals taken during CT are important because HR, BP, and rate pressure product are increased and remain high as the rest intervals between sets and exercises are decreased [17]. A reduced or lack thereof rest period between CT exercises would significantly increase the physiological stress at which an individual exercises while decreasing the overall exercise time.

TABLE 1: A five-week schedule for high-intensity circuit training (HICT) program. Dual emission X-ray absorptiometry (DXA).

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 1			Orientation	Before HICT blood work and DXA scan	Exercise session 1	
Week 2	Exercise session 2		Exercise session 3	Blood work	Exercise session 4	
Week 3	Exercise session 5		Exercise session 6	Blood work	Exercise session 7	
Week 4	Exercise session 8		Exercise session 9	Blood work	Exercise session 10	
Week 5	Exercise session 11		Exercise session 12	After HICT blood work and DXA scan		

Heart rate (HR), beats per minute (BPM), systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI).

The effect of CT on various physiological and anthropometric measurements in sedentary middle-aged subjects has been shown to be intensity dependent. Individuals who performed a 12-week high-intensity circuit training (HICT) program had the greatest reductions in body weight, percentage of fat mass, waist circumference, and blood lactate during a submaximal task and greater improvement in strength when compared to individuals who performed endurance training or low-intensity circuit training [18]. Middle-aged obese individuals who performed a 12-week (3, 50 min sessions) HICT program also had greater reductions in fat mass, blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and ApoB and increases in high-density lipoprotein cholesterol when compared to individuals who performed endurance training or low-intensity circuit training [16].

It would, therefore, be of great interest to determine the impact of a short duration HICT program on cardiovascular responses, body composition, blood profile, and physical performance. The proposed exercise program design consisting of the combination of resistance and callisthenic training through a short time commitment represents the innovative approach to challenge some of the current exercise paradigm used in primary health care models. In addition, the literature is sparse regarding metabolic change induced by HICT in obese population (see [10, 19, 20] for more details). The purpose of the current pilot study was therefore to determine how a 4-week HICT program would change key physiological health markers in sedentary obese males. The research question poses whether a 4-week HICT program would affect blood profile, resting HR, resting BP, body composition, and physical performance. Part of this data has been presented elsewhere in abstract form [21].

2. Methods

2.1. Participants. Eight apparently healthy sedentary male participants (34.3 ± 12.1 yrs, 179.1 ± 5.1 cm, 112.4 ± 20.1 kg) participated in the study. Eligibility of participants for the current study was based upon the following inclusion criteria: (1) ≥ 20 yrs of age, (2) being considered obese by the bray criteria determined from body fat percentage as measured by dual-energy X-ray absorptiometry (DXA) [22]

and (3) being healthy, without any serious metabolic, cardiovascular, or endocrine diseases and not taking any prescribed medications. Participants were considered sedentary because they performed only activities of daily living (ADL) and did not engage in any further exercise throughout the week. Participants were verbally informed of all procedures and, if willing to participate, read and signed a written consent form and a Physical Activity Readiness Questionnaire (PAR-Q) [23] prior to participation. The Memorial University of Newfoundland Human Investigation Committee approved this study (Health Research Ethics Authority number 11.319).

2.2. Experimental Design. Participants attended an orientation session two days prior to the start of the HICT program. During the orientation session, an investigator instructed the participants how to properly perform all resistance training exercises that were part of the HICT program. The investigator then assisted the participants in finding an 8–12 repetition maximum (i.e., the maximal amount of weight that could be lifted for 8–12 repetitions) for each resistance training exercise. One day prior to the start of the HICT program, blood samples and DXA scan measurements were collected. The next day the participants began the four-week HICT program. For the duration of the four-week HICT program, participants exercised on Monday, Wednesday, and Friday (a total of 12 exercise sessions). One day following the completion of the HICT program (after HICT), blood sample and DXA scan measurements were collected again. Blood samples were collected on Thursday of each week throughout the HICT program. Participants fasted for 12 hours prior to each DXA scan and each blood sample collection. The total time to complete all data collection was approximately 5 weeks (see Table 1 for a schematic of the schedule followed by participants). Throughout the HICT program, participants were asked not to make any change to their diets. This was done in order to determine the effect HICT would have on any measurements independent of any dietary alterations.

3. Exercise Protocol

Participants were instructed to follow the Canadian Society for Exercise Physiology preliminary instructions (no eating, drinking caffeine, smoking, or drinking alcohol for 2, 2, 2, or

6 hours, resp.) [23] before each exercise session. Upon arrival to the exercise facility, participants performed a five-minute warm-up consisting of functional body weight exercises using a combination of the exercises completed in the HICT protocol with minimal weight or step-ups and jumping jacks. Following the warm-up the participants completed the HICT protocol which included (1) squat, (2) bench press, (3) partial curl-up, (4) dead lift, (5) burpee, (6) bent over row, and (7) shoulder press (for exercise descriptions see [24]) under the supervision of an investigator. The participants would complete all exercises in order from 1 to 7 and then repeat the process for a total of 3 times (i.e., 3 sets). Verbal encouragement was given to all participants in an attempt to get them to work as hard and fast as possible with as minimal rest as possible between resistance training exercises and each set (i.e., very high work to rest ratio). Thus, the exercise protocol could have been considered a continuous HICT protocol.

The resistance training exercises were modified (easier or harder) throughout the HICT program depending on the capability (i.e., technique or fatigue) of the participant to complete any given exercise. Participants were asked to complete 8–12 repetitions for each resistance training exercise through the greatest range of motion as possible for each repetition. If the participant failed to reach 8 repetitions on a given set, the weight was reduced in the following set. If the participant reached >12 repetitions on a given set the weight was increased in the following set. The partial curl-up and burpee were completed at a varied number of repetitions for each set (i.e., until the participant reached fatigue).

4. Measurements

4.1. Heart Rate. HR was recorded to determine the training induced acclimation in resting HR over the HICT program and average training intensity (% of age predicted HR max (220-age)) each participant was exercising during each exercise session. A Polar (T-31, PolarElectro, Kempele, Finland) heart rate monitor was used to measure resting HR and HR during each exercise session for each participant. Throughout each exercise session HR was recorded after each set. The mean HR was then calculated for the whole exercise session.

4.2. Rating of Perceived Exertion. RPE was recorded as another measure of training intensity. Rating of perceived exertion was measured using Borg's RPE scale [25]. Participants rated their subjective exercise intensity from a scale of 6–20; six being equivalent to complete rest and 20 being equivalent maximum effort. RPE was recorded after each set throughout the exercise session. The mean RPE was then calculated for the whole exercise session.

4.3. Time to Completion. The total amount of time it took each participant to complete each exercise session was recorded. Time was recorded as soon as the participant started the exercise session and was stopped as soon as the participant completed the exercise session.

4.4. Total Work. TW for each exercise session was computed as the sum of the "weight lifted \times number of repetitions" for most of the exercises. Only the squat, bench press, dead lift, bent over row, and shoulder press exercises were used to calculate TW. Since we could not determine the amount of weight lifted for the burpee and partial curl-up these exercises were not included in the TW equation.

4.5. Blood Pressure. Resting BP was taken before and after HICT program using an electronic BP cuff (Physio Logic Auto Inflate BP Monitor; AMG Medical Inc., Montreal, QC). BP was recorded to determine training induced acclimation in resting systolic and diastolic BP over the HICT program. Participants were seated with two feet flat on the floor and the arm supported on a table. An appropriate size cuff was chosen and applied firmly to the participants left arm. The lower margin of the cuff was at heart level and two to three cm above the antecubital space.

4.6. Anthropometric and Body Composition Measurements. Participants were weighed to the nearest 0.1 kg in standardized clothing (Health O Meter, Bridgeview, IL). Height was measured using a fixed stadiometer (nearest 0.1 cm). Body mass index (kg/m^2) was calculated as weight in kilograms divided by participants height in meters squared. Body composition measurements were collected utilizing a DXA Lunar Prodigy (GE Medical Systems, Madison, WI). Version 12.2 of the enCORE software package (GE Medical Systems) was used for DXA analysis. DXA can produce an accurate measurement of adipose tissue within the body with a low margin of error. For this reason, DXA is considered to be one of the most accurate measurements of adiposity and is commonly used as a standard compared to less accurate field methods such as BMI. DXA measurements were performed on participants following the removal of all metal accessories, while lying in a supine position [26, 27]. Body composition measurements included lean body mass, percent lean body mass, fat mass, percent body fat (%BF), percent trunk fat (%TF), percent arm fat (%AF), and percent leg fat (%LF). The aforementioned measurements were used to compare changes in body composition from before to after HICT program. Quality assurance was performed on our DXA scanner daily and the typical CV was 1.3% during the study period. All participants in the study were between the ages of 20 and 59 with body fat percentage greater 30% which categorized them all as obese based upon the Bray criteria [22].

4.7. Biochemical Measurements. Fasting blood samples were obtained 5 times (see Table 2 for days in which blood was collected before, throughout, and after HICT program) from all participants by a registered nurse after 12 hours of fasting. Blood samples were stored at -80°C for subsequent analyses. The majority of biochemical markers remain stable under these conditions [28]. Blood markers including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and glucose were measured with the Lx20 analyzer (Beckman

TABLE 2: Blood sample measurements from baseline (before HICT program), weeks 1, 2, and 3 of the HICT program, and after the final exercise session in week 4 (after HICT program). Blood sample measurements and *P* values that are bolded indicate that there was a significant ($P < 0.05$) difference from before HICT program measurements. All data represent means \pm SD. Low-density lipoprotein (LDL), high-density lipoprotein (HDL), homeostasis model analysis (HOMA), insulin resistance (IR), and beta cell function (β).

Blood serum measurements	Baseline	Week 1—HICT	<i>P</i> value	Week 2—HICT	<i>P</i> value	Week 3—HICT	<i>P</i> value	Week 4—HICT	<i>P</i> value
Total cholesterol (mmol/L)	4.90 \pm 0.60	4.75 \pm 0.53	0.08	4.50 \pm 0.45	0.03	4.26 \pm 0.75	0.03	4.43 \pm 0.63	0.01
Triacylglycerol (mmol/L)	2.64 \pm 1.94	1.83 \pm 1.15	0.04	1.71 \pm 1.15	0.00	1.67 \pm 1.09	0.01	2.05 \pm 1.61	0.04
HDL cholesterol (mmol/L)	0.98 \pm 0.21	1.04 \pm 0.23	0.23	1.00 \pm 0.29	0.75	0.96 \pm 0.27	0.49	0.96 \pm 0.28	0.64
LDL cholesterol (mmol/L)	2.72 \pm 0.69	2.88 \pm 0.52	0.39	2.72 \pm 0.27	0.98	2.55 \pm 0.63	0.52	2.53 \pm 0.53	0.25
Glucose (mmol/L)	4.90 \pm 0.35	5.00 \pm 0.41	0.22	5.00 \pm 0.50	0.43	4.82 \pm 0.38	0.34	4.77 \pm 0.35	0.20
Insulin (pmol/L)	71.68 \pm 52.37	71.44 \pm 55.34	0.67	77.80 \pm 51.91	0.92	66.08 \pm 62.27	0.29	58.04 \pm 59.43	0.06
HOMA-IR	2.17 \pm 1.48	2.21 \pm 1.65	0.77	2.47 \pm 1.53	0.84	2.00 \pm 1.85	0.31	1.76 \pm 1.83	0.07
HOMA- β	177.32 \pm 156.28	156.48 \pm 132.67	0.40	161.71 \pm 132.40	0.72	156.79 \pm 154.06	0.22	141.11 \pm 133.50	0.06

Coulter Inc., Fullerton, CA). Blood insulin was measured by an immunoassay analyzer (Immulite; DPC, Los Angeles, CA). Insulin resistance and Beta cell function were interpreted using the homeostasis model analysis (HOMA), as described by [29]:

HOMA-IR

$$= \frac{[\text{Fasting Insulin (mU/L)} \times \text{Fasting Glucose (mmol/L)}]}{22.5}$$

$$\text{HOMA-}\beta = \left[\frac{20 \times \text{Fasting Insulin (mU/L)}}{\text{Fasting glucose (mmol/L)} - 3.5} \right]. \quad (1)$$

4.8. Statistical Analysis. All data analyses were conducted using SPSS statistics computing program version SPSS 18.0 (IBM Corporation, Armonk, NY, USA). To determine our sample size a power calculation was performed with a DSS Research statistical power calculator. Based on previous literature [14, 16, 18] a sample size of 8 was sufficient to achieve an alpha level of 0.05 and a power level of 0.80 to minimize the chance of making a type II error. Assumptions of sphericity were tested using Mauchley's test and if violated degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Before and after HICT program measurements for body composition and resting BP data were statistically analyzed using a paired *t*-test. A one-way ANOVA with repeated measures (i.e., time) was performed on dependent variables: resting heart rate (exercise sessions 1–12), RPE (exercise sessions 1–12), TW (exercise sessions 1–12), time to completion (exercise sessions 1–12), and biochemical measures (before weeks 1, 2, and 3 and one day after HICT program). Tukey LSD post hoc test was used to test for significant interactions within the repeated measures ANOVA. Levels of statistical significance for *t*-tests and *F*-ratios were considered statistically significant at the $P < 0.05$

level. Descriptive statistics for all data are reported as group means \pm SDs in text, table, and figures.

5. Results

5.1. Exercise Intensity. Total work, time to completion, HR, and RPE for each participant were measured during each exercise session. The average TW significantly increased ranging from 50.7% to 53.8% ($P < 0.04$) from exercise session one to exercise sessions 8–12 (Figure 1(a), primary *y*-axis). The time to completion was similar for all participants (~30 minutes) and did not significantly differ between exercise sessions ($P > 0.5$). On average, participants HR was maintained at $85 \pm 3.6\%$ of their average age predicted HR_{\max} throughout all 12 exercise sessions (Figure 1(a), secondary *y*-axis). Throughout the HICT program, the average RPE was 16.5 ± 2.5 ; however, there was no significant ($P > 0.3$) difference in participants' RPE for any exercise session (Figure 1(b)).

5.2. Resting Heart Rate and Blood Pressure. There was a continuous decrease in resting HR from exercise session to exercise session. Although decreases in resting HR were observed from day to day, significant ($P < 0.05$) decreases were not observed until the tenth exercise session compared to the first exercise session (Figure 2(a)). Resting HR decreased by 16.0% ($P < 0.05$) from before to after HICT program (Figure 2(b)). Systolic BP decreased by 5.5% ($P = 0.03$) from before to after HICT program (Figure 2(c)). Diastolic BP decreased by 3.4%, from before to after HICT program; however, this was not significant (Figure 2(d)).

5.3. Body Weight and Body Composition. There were no significant differences in the participant's body mass (112.4 ± 20.2 kg versus 111.1 ± 20.3 kg; $P = 0.26$) or body mass index ($P = 0.26$) (Figure 3(a)) from before to after HICT program. Participants body fat percentage significantly ($P < 0.01$)

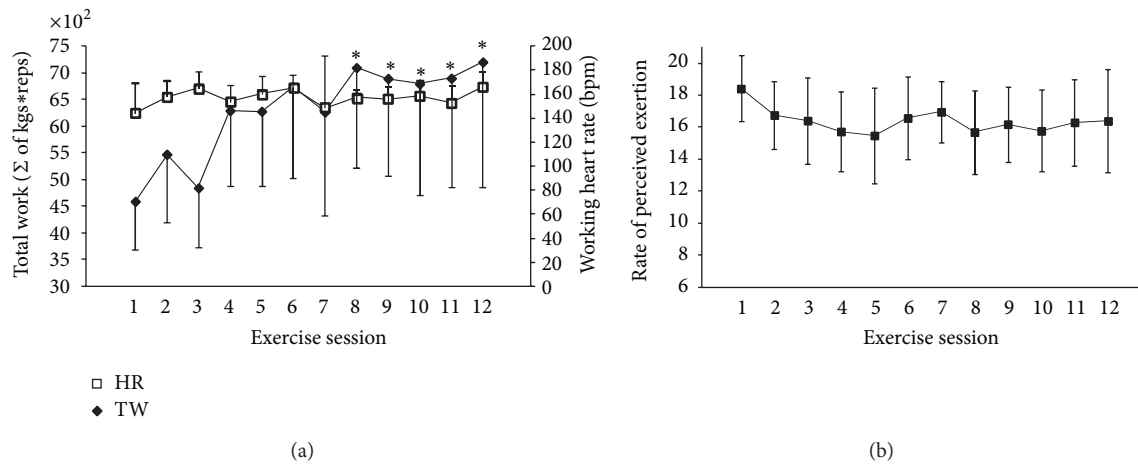


FIGURE 1: Measurements of exercise intensity. (a) The total work completed (primary y-axis) and the working heart rate (secondary y-axis). Significant ($P < 0.05$) differences between the first exercise session and exercise sessions 8–12 are indicated by an *. (b) Rate of perceived exertion for each exercise session throughout the HICT program. All data represent means \pm SD.

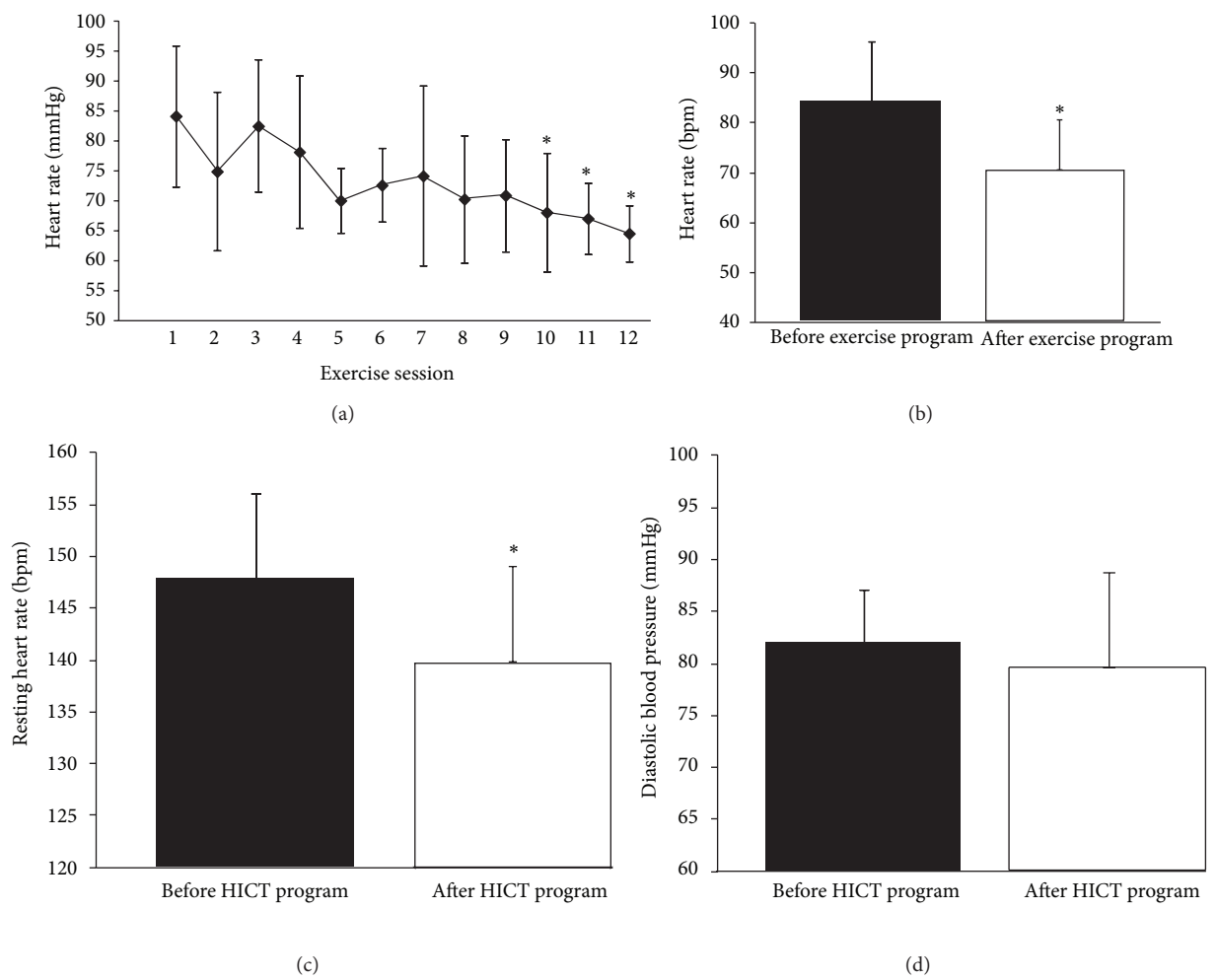


FIGURE 2: Heart rate and blood pressure measurements. (a) Resting heart rate for each participant measured prior to each exercise session. Significant ($P < 0.05$) differences between the first exercise session and exercise sessions 10–12 are indicated by an *. Differences between before and after HICT program for (b) resting HR, (c) systolic BP, and (d) diastolic BP. Significant ($P < 0.05$) differences are indicated by an * and all data represent means \pm SD.

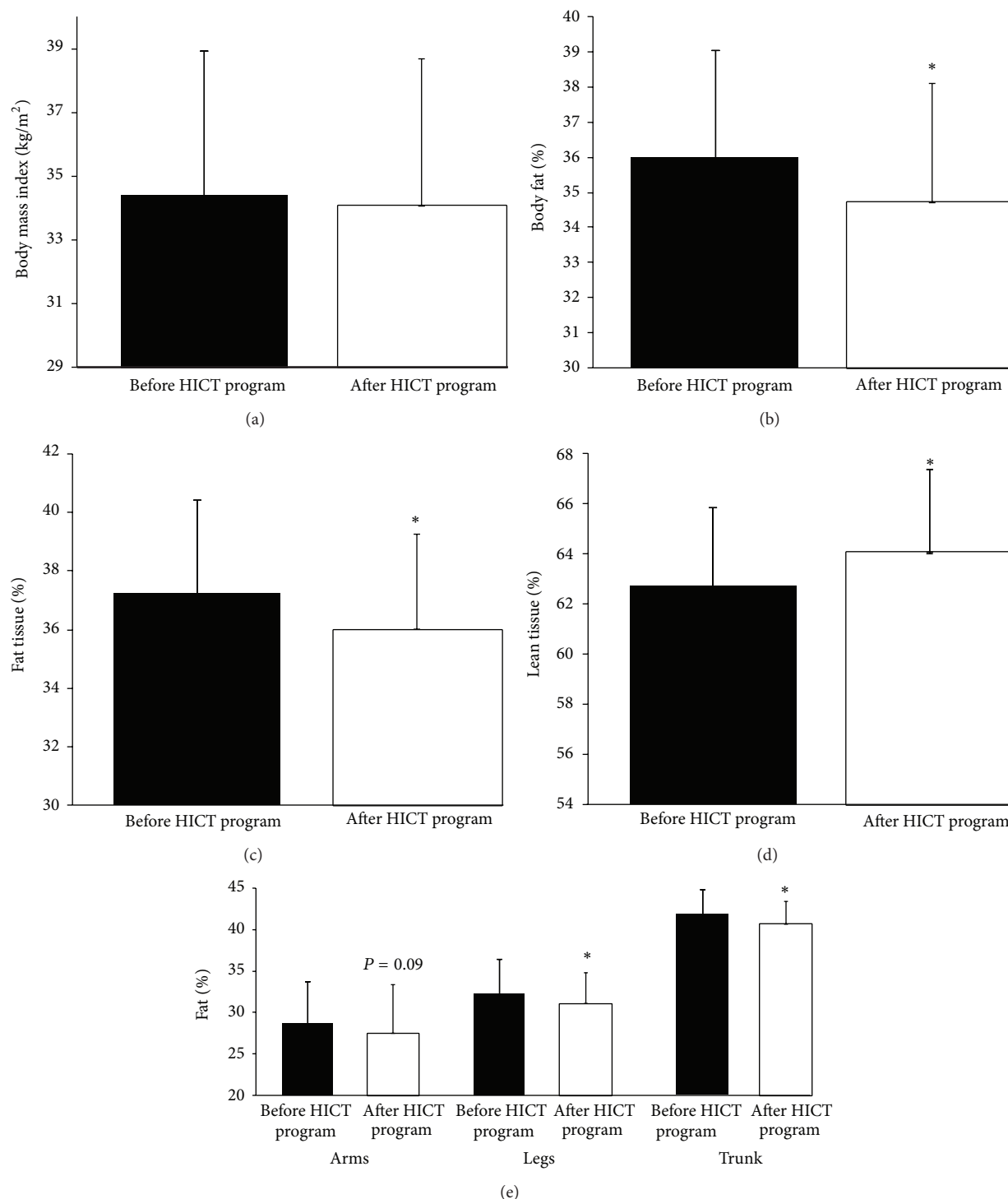


FIGURE 3: Body composition measurements. Differences between before and after HICT for (a) body mass index, (b) body fat percentage, (c) percentage of body fat tissue, (d) percentage of lean tissue, and (e) percent of fat found in the arm, leg, and trunk. Significant ($P < 0.05$) differences are indicated by an * and all data represent means \pm SD.

decreased by 1.6% from before to after HICT program (Figure 3(b)). Lean or fat mass did not change ($P = 0.26$ and $P = 0.1$, resp.) from before to after HICT program. However, when tissue was expressed as a percentage of total mass, the percent fat tissue significantly ($P < 0.01$) decreased

(Figure 3(c)) and the percent lean tissue significantly ($P < 0.01$) increased (Figure 3(d)) by 3.6% and 2%, respectively, from before to after HICT program. In addition there was a trend ($P = 0.09$) for a decrease in arm fat percentage of 4.7% and a significant ($P \leq 0.01$) decrease of 4% and 3% in leg and

trunk fat percentages, respectively, from before to after HICT program (Figure 3(e)).

5.4. Biochemical Measurements. All raw data for blood sample measurements are reported in Table 2. Fasting total blood cholesterol significantly ($P \leq 0.03$) decreased by 8.2%, 13%, and 10% at the second, third, and fourth weeks, respectively, of the HICT program compared to baseline (i.e., before HICT). Circulating triacylglycerol significantly ($P \leq 0.04$) decreased by 30.7%, 34.3%, 36.7%, and 22.4% at the first, second, third, and fourth weeks, respectively, of the HICT program compared to before HICT. There was a trend for insulin ($P = 0.06$), HOMA-IR ($P = 0.07$), and HOMA- β ($P = 0.06$) to decrease by 19.1%, 18.9%, and 18.2%, respectively, from baseline to the fourth week of the HICT program. The HICT program had no effect ($P \geq 0.2$) on fasting blood glucose, HDL cholesterol, and LDL cholesterol.

6. Discussion

To the best of the authors' knowledge, this was the first study involving obese males to show that high physiological stress delivered within such a short time window was enough to have an impact on cardiovascular responses, body composition, blood profile, and physical performance. The improvement observed in key health markers induced by our six-hour high-intensity exercise paradigm compares well with studies results using 4 to 8 times longer traditional aerobic, resistance, and circuit training programs (i.e., lasting 12–48 hours).

To monitor exercise intensity and psychophysiological stress during treatment, HR and RPE were measured. The overall participants HR values (see Figure 1(a)) compare well to other HICT studies [16, 18] and attest the high exercise metabolic rate induced by HICT. The 30 min exercise session mean RPE score reached ~16–17 throughout the training program (see Figure 1(b)) providing strong evidence that participants were exercising at a high intensity and were working at the same intensity during each exercise session throughout the HICT program. These outcomes were the result of performing 8–12 repetitions at ~70–80% of their one repetition maximum (1 RM) for every set throughout the HICT program.

The exercise program was designed to maintain repetition and set constant. The significant increase in total work (see Figure 1(a)) was, therefore, mainly due to an increased amount of weight lifted for each repetition (i.e., an increase in strength). A plethora of acute and chronic resistance training studies and reviews report increased strength and muscle mass in a healthy lean population [30–32]. However, obesity research examining the effects of short duration HICT compared to traditional resistance training on work output and/or strength is lacking. For instance, a normal weight sedentary population who performed a long duration HICT program did increase 6 RM leg and bench press performance, compared to the control group [18]. In the same vein, low-volume high-intensity cycling studies have reported chronic muscle metabolic responses comparable to traditional endurance

and resistance training [33–35]. In addition, high-intensity exercise provided greater cardiovascular adjustments than lower intensity exercise of the same volume of work [3, 36–38]. Based on the above-mentioned studies, one could have expected no positive effect on strength from such a short duration program; yet, in the current study, the total work (sum of reps \times weight) has increased by ~53% from exercise session 1 to exercise session 12 confirming the efficacy of HICT in inducing change in performance (see Figure 1(a)).

Increased BP and resting HR are commonly reported in research on obese individuals and are highly related to obesity-associated risk factors [39, 40]. In the current study six hours of a HICT program sufficed to significantly decrease systolic BP from a hypertensive level (147.9 mmHg) to a high-normotensive level (139.7 mmHg) [2] with no change in diastolic BP and to significantly lower resting HR from 84 bpm to 71 bpm. These results confirmed Paoli et al. [16] who observed a decrease in systolic blood pressure of overweight men using a much longer duration HICT program. Notwithstanding the fact that our exercise program was quite short, the results of the current study compare well with outcomes of chronic population exercise studies using different modes of exercise that were comparable [41] or greater in total exercise duration [4, 38, 42]. The significant decreased resting HR induced by our HICT program, however, contrasts with previous studies reporting no effect of traditional resistance training on this parameter in healthy population. This difference comes from the current HICT program that was designed to elicit high metabolic rate as mirrored by the elevated HR (see Figure 1(a)) during exercise sessions and that has resulted in a decreased resting HR similar to the response triggered by aerobic exercise training [7, 38]. The observed alterations might represent enhanced cardiovascular and haemodynamic responses during exercise and recovery [43] through adjustments in parasympathetic and sympathetic dual talk [44]. Independent of work volume, decreased resting HR and systolic BP were found following traditional resistance training in a cardiovascular disease population [41]. For instance, a recent meta-analysis [45] did report that in chronic and healthy populations high-intensity interval training was superior to induce positive chronic physiological responses ($\dot{V}O_2$, BP, HR, lipoproteins, glucose, insulin, cardiac function, oxidative stress, etc.) compared to moderate intensity continuous training. Paoli et al. [16, 18] have also shown that long duration HICT was superior compared to lower intensity circuit training for producing physiological responses similar to those previously listed. One of the relevant findings of the current study attests the efficacy of short duration HICT program in triggering cardiovascular adjustments.

Exercise has lately become of interest among health care professionals. Consequently, exercise physiologists increasingly include efficacy at the center of conceptualization and operationalization of a training program and start challenging exercise program design to optimize time and benefits. Our six-hour HICT program was actually designed to bring about improvement in health markers in a very short time window to comply with the new professional criteria. Although greater reductions in body weight and fat

mass and greater increases in lean body mass have been found in longer duration (3, 50 min sessions per week for 12 weeks) HICT studies involving middle-aged obese [16] and sedentary healthy [18] men, our exercise program design has had a significant impact on body composition of our participants. Overall, the participants in the current study gained 1.0 kg of lean mass and lost 1.5 kg of fat mass for a total healthy body composition shift of 2.5 kg and a closer look at the data set revealed significant changes in the fat percentage in the legs and the trunk and a trend towards significant changes in the arms. These results compare well to studies with exercise interventions ranging from 12 to 16 weeks [9, 12, 46] and confirm that HICT is as efficient in reducing body weight and body fat and in increasing lean body mass than low-intensity circuit training and endurance training. Interestingly, both short (the current study) and long duration [16, 18] HICT improved body composition in obese individuals who were not on any dietary restrictions.

In the current study, from the first week (~90 minutes of HICT) and second week (~180 minutes of HICT) and onward, triacylglycerol levels and cholesterol, respectively, decreased and remained decreased throughout the HICT program. Indeed, the reduction in cholesterol and triacylglycerol levels in the current study was of the same magnitude as that reported in the long duration HICT study [16]. Our findings support previous investigations reporting exercise induced decreases in lipids in the absence of dietary restrictions [16, 47, 48]. The results show that only twelve 30 min HICT sessions over a 4-week period can significantly attenuate insulin resistance in nondiabetic adult obese males, a finding that was not replicated in a longer duration low-frequency HICT program for type 2 diabetic patients [49]. Our data, along with others [50, 51], confirms that short duration high-intensity exercise is a time-efficient modality to significantly improve fitness and attenuate hyperglycemia. If the attenuation in insulin resistance is in fact primarily due to local muscle change in response to high-intensity resistance training, then perhaps the larger the number and size of muscles stimulated the greater the improvement in insulin action. Finally, our data demonstrates that HICT induced changes in blood markers (i.e., triacylglycerol, cholesterol, and insulin) are total exercise time dependent and that 6 hours of HICT was not long enough to induce changes in a variety of other blood markers (see Table 2) in obese males.

There were a few limitations in this study that should be considered. The sample population was healthy obese individuals with no comorbidities, which would probably be the one type of “at risk” population that could do the HICT program without problem. The type of training employed here and subsequent results may not be applicable to individuals with one or more chronic diseases. The sample size of the current research is small. However, the complexity of the training program did call for additional caution regarding participant recruitment and we did ensure that only well-motivated persons enrolled in our study, a procedure that has limited the number of participants. Although we did not use the appropriate HR maximum equations for determining exercise intensity in an obese population [52], we found no difference ($P = 0.9$) between HR based exercise intensities

by using the age predicted HR maximum and the obesity predicted HR maximum equation.

To reduce biomarker variability, blood samples were collected following 12 hr fasts and at the same time of day for each participant. Therefore, the changes in triacylglycerol levels seen in the current study were probably not due to one day of exercise but rather a cumulative effect of several exercise sessions as no differences were reported in a previous study between one bout of exercise at 24 and 48 hours [53]. Finally, although we did not place any dietary restrictions on the participants our HICT program did bring some change in key health markers. One can expect that combining a HICT program and a proper diet may have enhanced the current health outcomes.

The findings of this pilot study are very promising. We showed that a short duration HICT program could positively improve several physiological health markers in obese males. Most of the improvements are comparable to those found in much longer duration HICT, resistance training, and aerobic exercise programs. Since efficacy became the keyword in exercise programming and a “lack of time” is the most quoted deterrent for participating in an exercise program [3], short duration high-intensity exercise may come to the forefront as the exercise prescription of choice for healthy people and maybe for those who are at risk of chronic disease. However, further research is needed to evaluate the effect of HICT on at risk or chronic diseased populations.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Matthew B. Miller and Gregory E. P. Pearcey have contributed equally to the research.

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Research Article

High-Intensity Strength Training Improves Function of Chronically Painful Muscles: Case-Control and RCT Studies

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Aim. This study investigates consequences of chronic neck pain on muscle function and the rehabilitating effects of contrasting interventions. **Methods.** Women with trapezius myalgia (MYA, $n = 42$) and healthy controls (CON, $n = 20$) participated in a case-control study. Subsequently MYA were randomized to 10 weeks of specific strength training (SST, $n = 18$), general fitness training (GFT, $n = 16$), or a reference group without physical training (REF, $n = 8$). Participants performed tests of 100 consecutive cycles of 2 s isometric maximal voluntary contractions (MVC) of shoulder elevation followed by 2 s relaxation at baseline and 10-week follow-up. **Results.** In the case-control study, peak force, rate of force development, and rate of force relaxation as well as EMG amplitude were lower in MYA than CON throughout all 100 MVC. Muscle fiber capillarization was not significantly different between MYA and CON. In the intervention study, SST improved all force parameters significantly more than the two other groups, to levels comparable to that of CON. This was seen along with muscle fiber hypertrophy and increased capillarization. **Conclusion.** Women with trapezius myalgia have lower strength capacity during repetitive MVC of the trapezius muscle than healthy controls. High-intensity strength training effectively improves strength capacity during repetitive MVC of the painful trapezius muscle.

1. Introduction

Neck/shoulder pain is a frequent condition in the working population [1] and pain, tightness, and tenderness of the upper trapezius muscle—trapezius myalgia—are the most common type of chronic neck/shoulder pain [2, 3]. In a study among elderly female computer workers with neck/shoulder pain 38% were clinically diagnosed with trapezius myalgia [3]. In another study among office workers with frequent neck/shoulder pain three out of four experienced tenderness by palpation of the upper trapezius muscle [4]. Trapezius myalgia is associated with pathophysiological changes, such as increased occurrence of ragged red fibers, moth eaten fibers, and cytochrome oxidase negative type I fibers [5, 6]. Using the microdialysis technique, increased concentration

of the algescic substance serotonin during work, stress, and rest has also been shown [7]. Recent studies combining muscle biopsies and microdialysis with gel electrophoresis and mass spectrometry identified several proteins involved in inflammatory processes in myalgic trapezius muscles compared with healthy controls [8, 9]. Women with trapezius myalgia also have reduced capillarization of type I muscle fibers [10], increased proportion of poorly capillarized type I megafibers [11], impaired regulation of microcirculation locally in the painful trapezius muscle [12–14], and reduced capacity of carbohydrate oxidation [15]. These factors lead to elevated anaerobic metabolism and fatigue during repetitive work [16, 17].

In addition, trapezius myalgia negatively impacts muscle functioning. Compared with healthy controls, women with

trapezius myalgia show decreased maximal voluntary force, rapid force, motor control, endurance, and neck flexibility [18–22]. Trapezius myalgia has also been associated with an inability to properly relax the muscle between repeated contractions [23], which may aggravate development of fatigue. Thus, prevention as well as rehabilitation of neck/shoulder pain has focused on improving different components of physical function such as the ability to relax the muscles using biofeedback training [24, 25], muscle coordination training [26], muscle strength using high-intensity resistance training [26–28], endurance using repeated low-intensity contractions [26, 27], fitness training [29], and flexibility using stretching [27]. Among these training modalities strength training appears particularly effective in reducing pain and increasing muscle strength in trapezius myalgia [28]. However, transfer effects of strength training to improve work capacity of the painful trapezius muscle have only been scarcely investigated [26]. This is a potential important aspect, as daily job tasks require repetitive muscle contractions inducing a certain level of fatigue, for example, repetitive arm movements during assembly line work or keyboard typing. Studying the effect of strength training on strength-endurance during repetitive and fatiguing contractions therefore seems pertinent.

A contrasting approach to specific strength training could be to train large muscles distant from the painful site, for example, by general fitness training performed as leg cycling. Previous research in other populations has indicated physiological adaptations in sites distant from the trained muscles [30, 31]. Increased blood flow to the forearms [32] and nonworking limb [33] has also been shown in response to leg exercise. Based on these studies, general fitness training performed as leg cycling may also improve endurance of the painful trapezius muscle.

The aims of the present study were (1) in a case-control design to compare muscle function during fatiguing muscle contractions in women with trapezius myalgia and healthy controls and (2) in a randomized controlled trial to investigate the effect of contrasting types of physical rehabilitation in women with trapezius myalgia on muscle function during fatiguing muscle contractions. Additionally, analyses of electromyographic recordings and muscle biopsies were included to investigate neural and muscular adaptations. We hypothesized that specific strength training and general fitness training would be superior to the reference intervention with regard to improved muscle function.

2. Methods

2.1. Study Design and Participants. The study design, recruitment of participants, randomization of 48 women, and main results have been described in detail previously [14, 28]. In the present case-control study, 42 women with trapezius myalgia (MYA, mean \pm SD: 44 \pm 8 yrs, 165 \pm 6 cm, 72 \pm 15 kg, and days with neck pain during previous year 219 \pm 19 days) and 20 women comparable with regard to job-type, age, weight, and height but without neck muscle complications (CON, mean \pm SD: 45 \pm 9 yrs, 167 \pm 6 cm, 70 \pm 11 kg, and days with neck pain during previous year 5 \pm 6 days) participated. Exclusion

criteria were serious conditions such as previous trauma, life threatening diseases, whiplash injury, cardiovascular diseases, or arthritis in the neck and shoulder. All participants were recruited from workplaces with monotonous and repetitive work tasks, mostly office- and computer-work. All females in MYA were clinically diagnosed with trapezius myalgia, where the main criteria for a positive diagnosis were (1) chronic pain in the neck area, (2) tightness of the upper trapezius muscle, and (3) palpable tenderness of the upper trapezius muscle [28]. In the 10-week intervention study, the 48 women with trapezius myalgia were randomly allocated in balanced design accounting for similar age, BMI, and neck/shoulder trouble to three different 10-week interventions, but 6 dropped out initially in the REF group resulting in 42 women in this study. The random allocation was concealed; that is, the researcher who determined the eligibility of the subjects was unaware which group a subject was to be allocated to. Unfortunately, the timewise successive balanced recruitment resulted in a somewhat smaller REF group, for example, due to withdrawal of 6 participants who initially stated they would volunteer for the study.

All subjects were informed about the purpose and content of the project and gave written informed consent to participate in the study, which conformed to the Declaration of Helsinki and was approved by the Local Ethical Committee (KF 01-138/04). The study was registered in the International Standard Randomised Controlled Trial Number Register (ISRCTN87055459).

2.2. Measurements and Data Acquisition. Muscle endurance was measured during consecutive isometric shoulder elevations using a custom-built setup with a steel frame, a chair, and attached force dynamometers (Figure 1). The participant was sitting upright in the height-adjustable chair, and two Bofors dynamometers were placed bilaterally 1 cm medial to the lateral edge of the acromion with the direction of force being upward [34]. Prior to the endurance test, the participant performed 3 maximal voluntary isometric contractions (MVC) to determine peak force. The participant was then instructed to perform 100 consecutive cycles of 2-second MVC followed by 2-second relaxation. Figure 1 shows the square wave on the computer screen providing visual feedback instructing the participant when to contract and when to relax, with the target value of the square wave set to the peak force determined prior to the endurance test. The participant was instructed to contract as hard and fast as possible when the signal of the square wave went from zero to max and to relax immediately and completely when the signal went from max to zero. The 100 contractions were completed in 6 minutes and 40 seconds.

Electromyography (EMG) signals were recorded synchronously from the upper trapezius muscle with a bipolar surface EMG configuration (Neuroline 720 01-K, Medicotest A/S, Ølstykke, Denmark) and an interelectrode distance of 2 cm [35]. The electrodes were positioned according to SENIAM guidelines [36]. The skin was abraded prior to applying the electrodes to ensure an impedance of less than 10 k Ω (typically the impedance was 1–2 k Ω). If the impedance was higher than 10 k Ω the procedure was repeated until

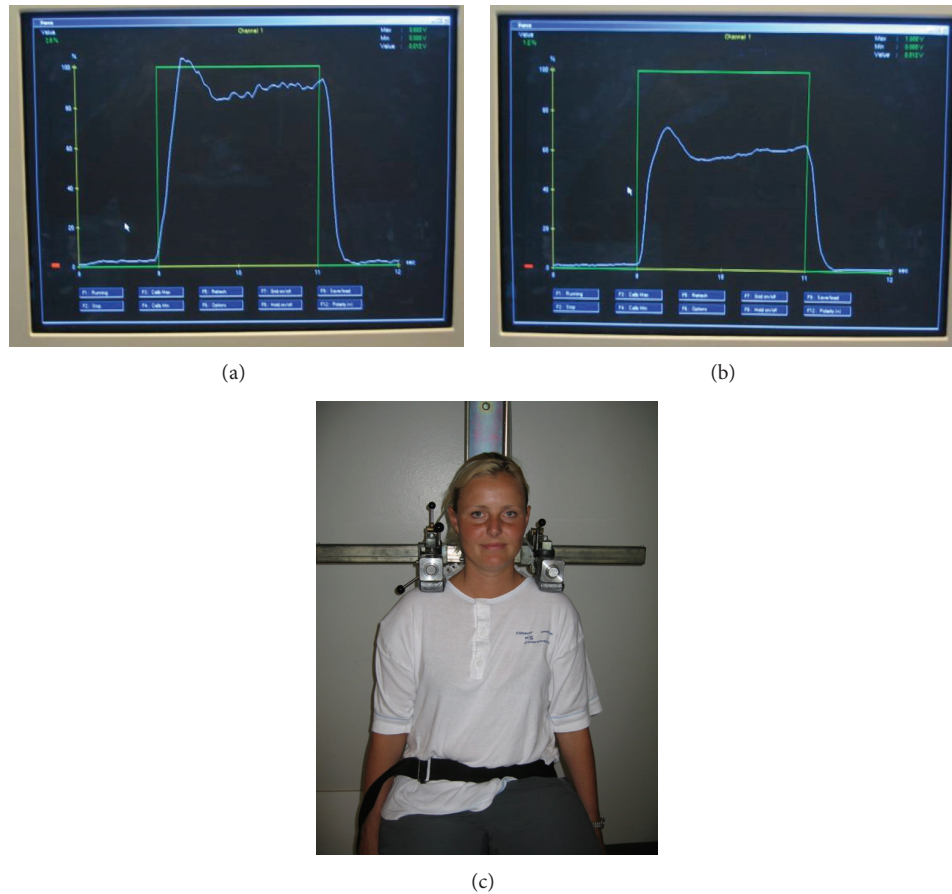


FIGURE 1: Illustration of experimental setup, the square wave signal (green tracing), and a typical force signal (white tracing) in the beginning (left) and during the end (right) of the 100 consecutive contractions.

impedance was less than $10\text{ k}\Omega$. The EMG electrodes were connected directly to small preamplifiers located near the recording site. The raw analogue EMG signals were led through shielded wires to instrumental differentiation amplifiers, with a bandwidth of 10–400 Hz and a common mode rejection ratio better than 100 dB. Force and EMG signals were sampled synchronously at 1000 Hz using a 16-bit A/D converter (DAQ Card-AI-16XE-50, National Instruments, USA) and stored on a laptop for further analysis.

2.3. Data Analysis. Data were analyzed only for the signals from the most painful shoulder. In case of similar pain intensities in both shoulders the dominant side was used for the analyses. During later offline analyses, the force signal was low-pass filtered at 10 Hz, and then three parameters were calculated for each of the 100 MVCs: (1) peak force, determined as the maximal force value within each cycle, (2) rate of force development (RFD) determined as the maximal positive slope over 100 msec of the force signal during the beginning of each MVC, and (3) rate of force relaxation (RFR) determined as the maximal negative slope over 100 msec of the force signal during the end of each MVC. All RFR values were subsequently multiplied by -1 to ease comparison with RFD.

Likewise, the raw EMG signals were filtered using linear EMG envelopes, which consisted of (1) high-pass filtering at

10 Hz, (2) full-wave rectification, and (3) low-pass filtering at 10 Hz. The filtering algorithms were based on a fourth-order zero phase lag Butterworth filter [37]. From the filtered EMG signal the following parameter was calculated for each of the 100 MVCs: (1) peak EMG, determined as the maximal value of the filtered signal during the top phase of the square signal, that is, when muscle force is peaking, (2) integrated EMG during the first 1/2 second of the top phase of the square signal, that is, during the very beginning of muscle contraction, and (3) resting EMG determined as the average value of the filtered signal during the mid 1/2 second of the bottom phase of the square signal, that is, during relaxation between contractions.

The power spectral density of the EMG signals was calculated as the median power frequency (MPF) in epochs of 1000 ms in the midphase of each of the 100 contractions. The power density spectra were estimated by Welch's averaged, modified periodogram method in which each epoch was divided into eight Hamming windowed sections with 50% overlap.

2.4. Muscle Biopsies. Using the needle biopsy technique, muscle biopsies were obtained ultrasound guided from the upper trapezius muscle at the midbelly between the 7th cervical vertebrae and the acromion. The tissue samples

were mounted with Tissue-Tek within 2-3 min, frozen in isopentane precooled with liquid nitrogen, and stored in a freezer at -80°C until processed. All biopsy samples were given a unique identification number and blinded. Transverse serial sections ($10\text{ }\mu\text{m}$) of the embedded muscle biopsy were cut in a cryostat (Microm, Germany) (22°C) and mounted on glass slides. Standard ATPase analysis was performed after preincubation at pH values of 4.37, 4.61, and 10.30 [38]. The biopsy sections were visualized on a computer screen using a Carl Zeiss light microscope (Zeiss Axiolab), a JVC high-resolution color digital camera (JVC, TK-C1381EG), and an 8-bit Matrox Meteor Framegrabber (Matrox Electronic Systems, Quebec, Canada). Quantitative analysis of all muscle samples for fiber type percentage, fiber cross-sectional area (CSA), capillaries per fiber (CAF), and capillaries per fiber CSA (CAFA) was performed using a digital image analysis program (TEMA 1.04, Scanbeam, Hadsund, Denmark). All values are reported for types I and II fibers separately. The results on fiber type percentage (case-control study), fiber type area percentage (intervention study), CSA (case-control and intervention study), and CAF and CAFA (case-control study) have been reported previously [11, 39] and are reported here only for comparison with the results from the endurance test. Results from the intervention study for fiber type percentage, CAF, and CAFA have not been reported previously and are reported here as original data.

2.5. Interventions. After the case-control study, the 42 women with trapezius myalgia were randomly allocated to three different 10-week interventions. The specific strength training group (SST, $n = 18$) performed five dumbbell exercises specifically for the shoulder and neck muscles (shoulder abduction, shoulder elevation, 1-arm row, reverse flies, and upright row) for 20 min three times a week. The high level of activity of the neck and shoulders muscles using these exercises has been documented elsewhere [40]. Three of the five exercises were performed during each session for three sets of each exercise using relative loadings of 8–12 repetitions maximum (RM). The strength training schedule followed principles of progressive overload and periodization as recommended by the ACSM [41]. The general fitness training group (GFT, $n = 16$) performed leg-bicycling in an upright position with relaxed shoulders on a stationary ergometer at relative loadings of 50% to 70% of maximal oxygen uptake for 20 min three times a week. The loading was estimated based on relative workload = (working heart rate – resting heart rate)/(max heart rate – resting heart rate), where resting heart rate was set to 70 bpm and max heart rate was estimated as $220 - \text{age}$ [42]. The reference group (REF, $n = 8$) received information concerning health promotion for one hour per week but were not offered any physical training. Unfortunately, the timewise successive balanced recruitment resulted in a somewhat smaller REF group compared with the two other groups, for example, due to withdrawal of participants who initially stated they would volunteer for the study.

2.6. Statistics. In the case-control study, differences between MYA and CON were tested with two-way ANOVA (Proc

Mixed of SAS). The dependent variables were peak force, RFD, RFR, and peak EMG, respectively. Independent fixed factors included in the model were *group* (MYA, CON), *number* (100 contractions), and *group by number* interaction.

In the intervention study, differences over time between the three groups were tested with repeated measures two-way ANCOVA (Proc Mixed of SAS). The dependent variables were the changes from baseline to follow-up in peak force, RFD, RFR, and peak EMG, respectively. Independent fixed factors included in the model were *group* (GFT, SST, and REF), *number* (100 contractions), and *group by number* interaction. The baseline value of the dependent variable was included as a covariate due to the numerical differences visualized in Figure 2. Participant was entered in the model as a nested random effect using the *repeated* statement.

The alpha level was set to 0.05, and results are reported as means \pm SE in the figures and as means and 95% confidence intervals in the text.

Finally, when statistically significant changes were found we calculated effect sizes as Cohen's d (difference from baseline to follow-up divided by the pooled standard deviation at baseline) [43]. According to Cohen, effect sizes of 0.20 are small, 0.50 moderate and 0.80 large.

3. Results

3.1. Case-Control Study. There was a significant *group* effect for all three force parameters ($P < 0.001$). Post hoc analyses showed that peak force, rate of force development, and rate of force relaxation were lower in MYA compared with CON (Figure 2, *left*). There was a significant *group* effect for two of the four EMG parameters. Post hoc analyses showed that peak EMG and rate of EMG rise were lower in MYA compared with CON (Figure 3, *left*). There was no significant *group* effect for resting EMG (Figure 3, *left*) or MPF (Figure 4, *left*). There was no *group by number* interaction; that is, the slope over the 100 repetitions did not significantly differ between the two groups, although there was a borderline *group by number* interaction for MPF ($P = 0.05$).

Capillarization per fiber as well as per fiber area did not significantly differ between MYA and CON, neither for type I nor type II fibers (Table 1).

3.2. Intervention Study. There was a significant *group* effect for the change from baseline to follow-up for all three force parameters ($P < 0.01$ – 0.001). Post hoc analyses showed that the strength training group improved significantly more than the two other groups for peak force (SST versus GFT 70 N [95% CI 35–105], SST versus REF 50 N [95% CI 7–93]), rate of force development (SST versus GFT $346\text{ N}\cdot\text{s}^{-1}$ [95% CI 97–595], SST versus REF $464\text{ N}\cdot\text{s}^{-1}$ [95% CI 156–772]), and rate of force relaxation (SST versus GFT $-378\text{ N}\cdot\text{s}^{-1}$ [95% CI -233 – (-523) , SST versus REF $-323\text{ N}\cdot\text{s}^{-1}$ [95% CI -143 – (-503)] (Figure 2, *right*). The effect sizes for these changes in the SST group were 0.61, 0.96, and 0.90 for peak force, rate of force development, and rate of force relaxation, respectively. Thus, the effects of SST can be considered moderate (peak force) to large (rate of force development and rate of force relaxation).

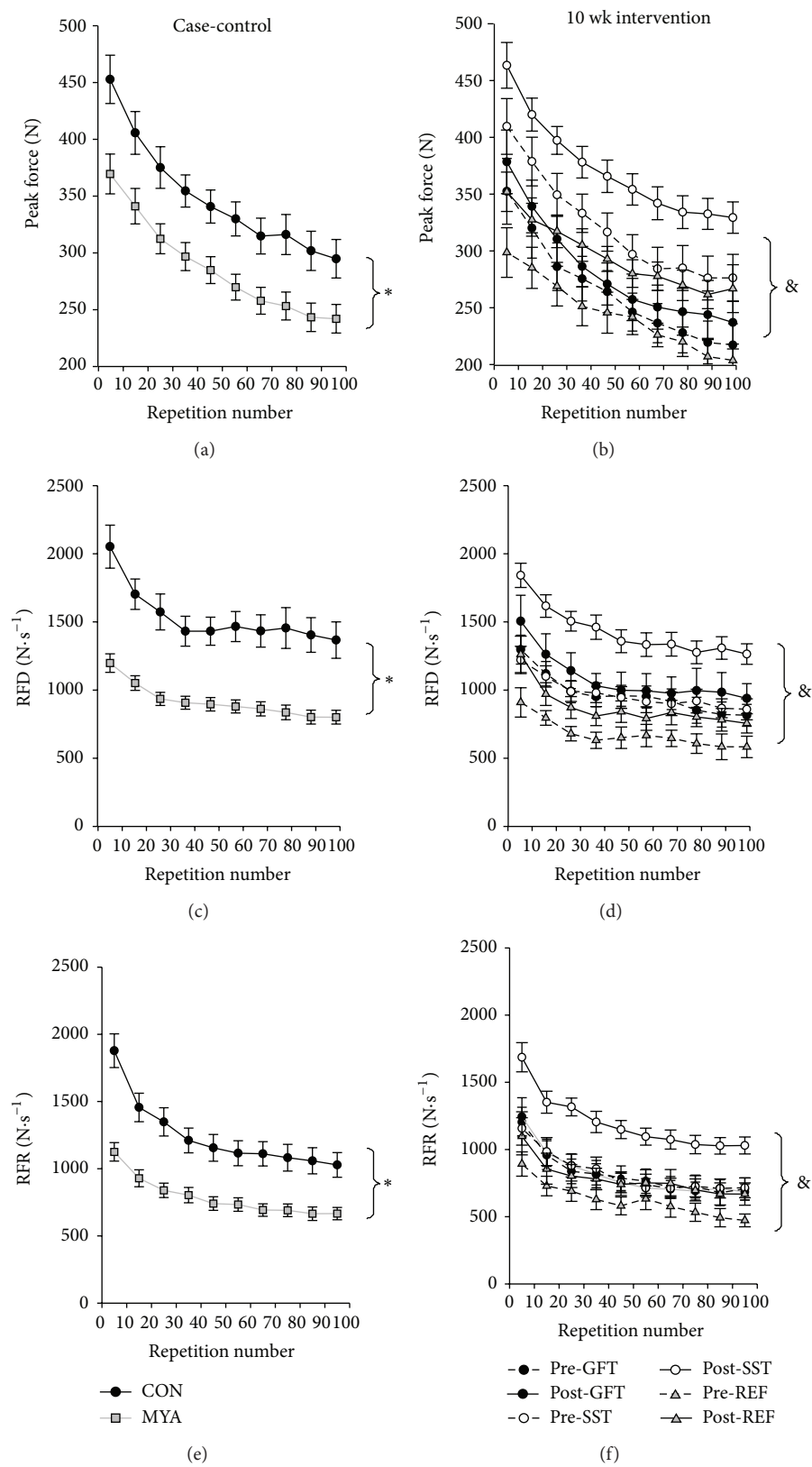


FIGURE 2: Case-control (left) and intervention (right) results of peak force (top), rate of force development (RFD) (mid), and rate of force relaxation (RFR) (bottom). *Significant group effect; $P < 0.001$ and $P < 0.01$.

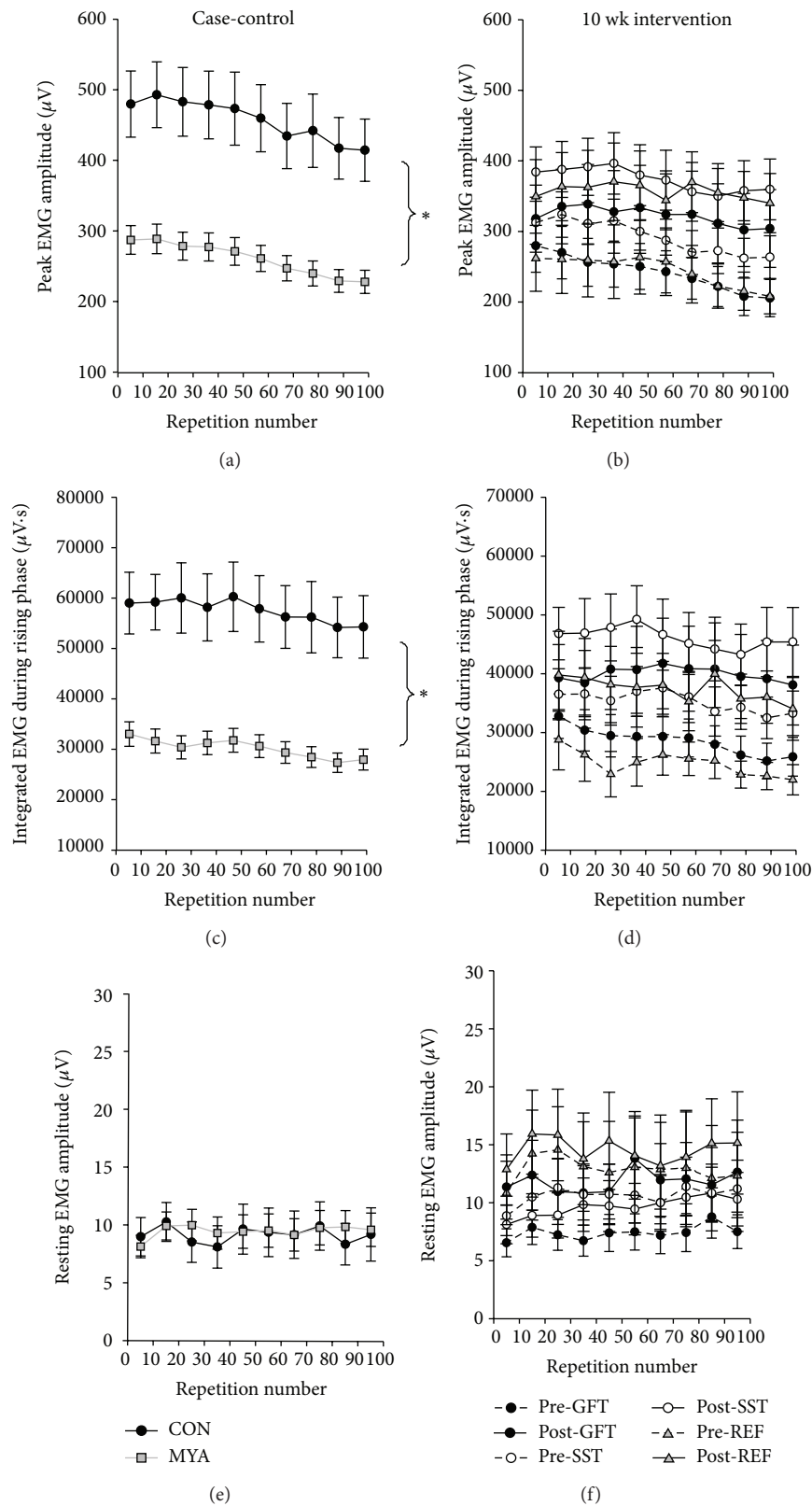


FIGURE 3: Case-control (left) and intervention (right) results of peak EMG (top), integrated EMG during the rising phase of contraction (mid), and resting EMG (bottom). *Significant group effect; $P < 0.001$ and $P < 0.01$.

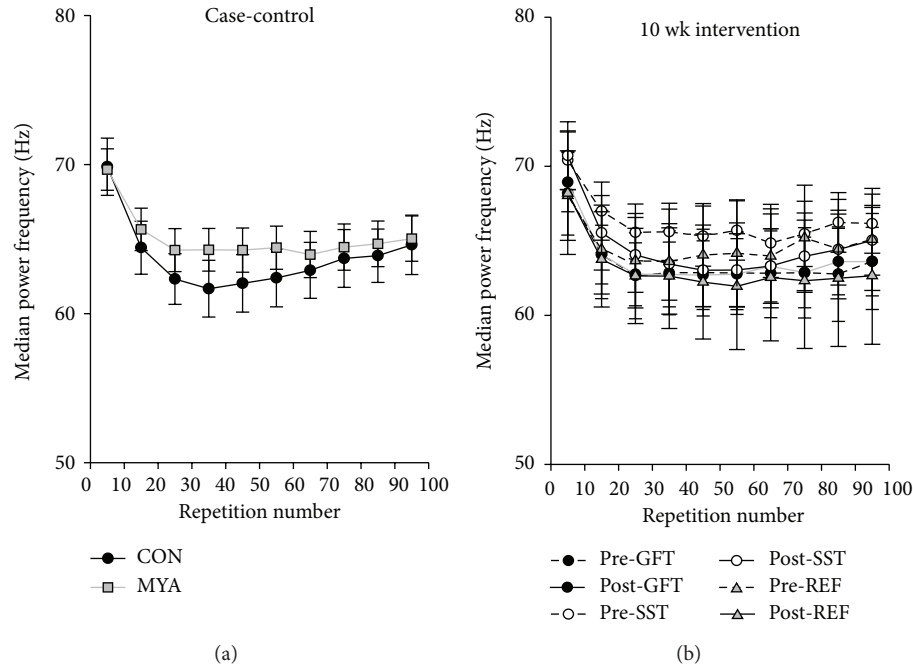


FIGURE 4: Case-control (left) and intervention (right) results of median power frequency (MPF) of the EMG signal.

TABLE 1: Muscle fiber cross-sectional area, fiber type percentage, capillaries per fiber (CAF), and capillaries per fiber area (CAFA) in healthy controls (CON) and women with trapezius myalgia (MYA) at baseline and before and after 10-week intervention in the specific strength training (SST), general fitness training (GFT), and reference (REF) groups.

	Area (μm^2)		Fiber type percentage (%)		Capillaries per fiber (CAF)		Capillaries per fiber area (CAFA)	
	Type I	Type II	Type I	Type II	Type I	Type II	Type I	Type II
CON	5057 \pm 1120	4000 \pm 1104	67 \pm 11	33 \pm 11	4.23 \pm 0.74	3.15 \pm 0.72	0.89 \pm 0.15	0.84 \pm 0.17
MYA	5193 \pm 1110	3501 \pm 977	69 \pm 11	31 \pm 11	4.12 \pm 0.87	2.79 \pm 0.70	0.83 \pm 0.14	0.86 \pm 0.20
REF								
Before	4941 \pm 399	3334 \pm 489	66 \pm 13	34 \pm 13	3.72 \pm 0.49	2.41 \pm 0.33	0.81 \pm 0.14	0.78 \pm 0.14
After	5299 \pm 1134	3471 \pm 684	66 \pm 14	34 \pm 14	3.97 \pm 0.53	2.60 \pm 0.61	0.83 \pm 0.18	0.78 \pm 0.16
GFT								
Before	5555 \pm 1201	3794 \pm 796	69 \pm 11	31 \pm 11	4.39 \pm 0.80	3.10 \pm 0.51	0.85 \pm 0.19	0.89 \pm 0.25
After	5108 \pm 1030	3612 \pm 1070	72 \pm 11	28 \pm 11	4.18 \pm 0.43	2.93 \pm 0.57	0.85 \pm 0.15	0.87 \pm 0.34
SST								
Before	5043 \pm 1294	3439 \pm 1331	69 \pm 12	31 \pm 12	4.15 \pm 1.09	2.80 \pm 0.95	0.85 \pm 0.13	0.88 \pm 0.22
After	5516 \pm 1188 [#]	4133 \pm 1145 [§]	70 \pm 10	31 \pm 10	4.53 \pm 0.82 [#]	3.31 \pm 0.64 [§]	0.88 \pm 0.13	0.85 \pm 0.17

[#]Tendency for increase from baseline to follow-up in SST, $P < 0.10$.

[§]Significant increase from baseline to follow-up in SST, $P < 0.05$.

There was no significant *group* effect for the change from baseline to follow-up for any of the EMG parameters (Figure 3, *right*, and Figure 4, *right*). There was no *group by number* interaction for the change from baseline to follow-up; that is, the change in the slope over the 100 repetitions did not significantly differ between the three intervention groups.

Capillarization per fiber as well as muscle fiber cross-sectional area increased significantly in the SST group for type II fibers ($P < 0.05$) and tended to increase for type I fibers ($P < 0.10$). In SST, capillarization per fiber area

remained unchanged in both types I and II fibers (Table 1). No significant changes occurred in the two other groups.

3.3. Test-Retest Reliability. Test-retest reliability of the outcome measures was not determined prior to the study. However, we performed reliability analyses after the study using the data from the two groups that did not respond to the intervention, that is, the GFT and REF groups. For these analyses the values for each subject were averaged for the 100 contractions at baseline and follow-up, respectively.

The intraclass correlation coefficient (ICC) between baseline and 10-week follow-up was 0.85 for peak force, 0.70 for rate of force development, and 0.85 for rate of force relaxation.

3.4. Post Hoc Power Analysis. Due to the nonsignificant changes in the EMG parameters we performed a post hoc power analysis using the EMG data (averaged for the 100 contractions for each subject) from the two groups that did not respond to the intervention, that is, the GFT and REF groups. At baseline peak EMG was 244 μ V (mean value) and the standard deviation of the change from baseline to follow-up was 139 μ V. Requesting 80% power to detect 20% difference from baseline to follow-up with a type I error probability of 5% would then require 66 subjects in each group. Correspondingly, with only 14 subjects in each group the power to detect 20% difference is only 20.8%; that is, it is likely that 4 in 5 studies with similar sample size would report null findings.

4. Discussion

The main findings of the present study were (1) that women with trapezius myalgia showed reduced force capacity during repetitive maximal contractions of the trapezius muscle compared with healthy controls (case-control study) and (2) that 10 weeks of high-intensity specific strength training led to improved force capacity of the trapezius muscle in women with trapezius myalgia. By contrast, leg cycling did not improve trapezius muscle function. These results along with neural and muscular findings are discussed in the following.

In the case-control study, peak force, rate of force development, and rate of force relaxation as well as peak EMG and integrated EMG during the rising phase of contraction were lower in women with trapezius myalgia compared with healthy controls. We have previously shown—in the same group of subjects—that peak force and rate of force development during a single maximal voluntary contraction are lower in women with trapezius myalgia [21]. In the present study we elaborate on these findings by showing that all these force parameters are lower throughout all 100 contractions. However, the slopes of curves for the peak force values did not differ between the groups. This finding suggests that lower strength-endurance capacity in women with trapezius myalgia is related to the generally lower level of muscle strength—generally requesting a higher relative load during daily life and occupational tasks [14]—rather than faster development of fatigue.

Some of our case-control results contrast previous findings. In contrast to the findings by Larsson and coworkers [10] we did not find reduced capillarization of type I muscle fibers in women with trapezius myalgia compared with healthy controls. This is surprising since we have also in previous studies found a decreased oxygenation in women with trapezius myalgia compared to healthy controls during a more functional and submaximal test using a pegboard task [14]. This may suggest that impaired regulation of microcirculation, rather than reduced capillarization, may contribute to development of pain and fatigue during repetitive work tasks in women with trapezius myalgia.

Also, based on the EMG measurements we found that women with trapezius myalgia and healthy controls had similar ability to relax the muscles, that is, the same level of EMG amplitude, between repeated contractions, which contrast the EMG findings by Elert and coworkers [23]. However, there are methodological differences between the studies which make direct comparison difficult. Elert and coworkers used dynamic contractions and defined the ability to relax the trapezius as the ratio between EMG amplitude of the eccentric (relaxation phase) and concentric phase (contraction phase) of the 100 contractions. As a ratio depends both on the numerator and denominator it can increase simply by decreased maximal EMG during each concentric contraction, which makes the results by Elert and coworkers difficult to interpret.

Different types of normalization of the EMG signal are typically performed to avoid the inherent variance associated with EMG amplitude. By contrast, we did not normalize the EMG amplitude to a maximal voluntary contraction (MVC) as neck/shoulder pain inhibits central drive and thereby the EMG signal during maximal contraction [21, 22, 44]. Thus, normalizing the EMG signal to a maximal contraction would give erroneous normalized values when comparing individuals with and without pain and also when comparing data before and after an intervention that decreases pain. On the other hand, comparing nonnormalized EMG amplitudes between groups is also associated with limitations, such as variance due to electrode placement and thickness of subcutaneous fat. Therefore we carefully placed the EMG electrodes at the same part of the muscle between participants and test sessions by using the seventh cervical vertebrae and the acromion as reference points in accordance with SENIAM guidelines [36]. Further, we have previously reported that there was no difference between MYA and CON in thickness of the subcutaneous layer of fat above the trapezius muscle, and neither did this change significantly during the 10-week intervention period [45]. Thus, our results indicate that women with trapezius myalgia have the same ability to relax between muscle contractions.

In spite of similar resting EMG between contractions, the force measurements showed that relaxation from maximal to zero muscle contraction was slower, that is, lower rate of force relaxation, in women with trapezius myalgia than healthy controls. Thus, although women with trapezius myalgia have the ability to fully relax the muscles, it takes longer than in healthy controls. Although speculatively, this may be related to altered Ca^{2+} kinetics of myalgic muscles. Interestingly, Green and coworkers found a compromised sarcoplasmic reticulum Ca^{2+} -ATPase activity, Ca^{2+} -uptake, and Ca^{2+} -release in a case-series study involving women with myalgia [46]. A slower relaxation of myalgic muscles may have negative implications for high pace work tasks where the time for recovery between contractions is minimal.

The intervention study showed that high-intensity strength training improves both maximal and rapid force capacity as well as the ability to rapidly relax—that is, rate of force relaxation—after each contraction. We have previously reported a marked reduction (79%) of pain along

with increased maximal and rapid force capacity of single maximal voluntary contractions in response to the 10-week high-intensity strength training intervention [28, 39, 47]. The present study elaborates on these findings by showing that muscle function is improved during repetitive maximal muscle contractions. This may have important practical implications as many job tasks require repetitive muscle contractions, such as keyboard typing or repetitive arm movements during assembly line work. Further, previous analyses have shown increased carbohydrate oxidative capacity after specific strength training in women with trapezius myalgia [15], which may also help to explain the ability to sustain a high force development during repetitive contractions. Apart from improved muscle function during repetitive job tasks, the present study also demonstrated significant myofiber hypertrophy and increased capillarization in response to 10 weeks of specific strength training. Thus, these muscular adaptations may partly explain the present findings, although we cannot exclude the existence of neural adaptations mechanisms. Despite the fact that neither of the EMG parameters changed significantly between the intervention groups, the strength training group had the numerically highest EMG amplitude values at 10-week follow-up. Post hoc power analysis showed that 66 subjects in each group would be required to detect a 20% difference in peak EMG between groups from baseline to follow-up. Therefore, the present study was underpowered to detect significant changes due to the inherent high variability of the EMG measurements, making significant results more difficult to obtain with a small sample size.

Median power frequency of the EMG signal decreased as expected during fatiguing contractions (Figure 4). This was evident both in healthy controls and women with trapezius myalgia at baseline and follow-up. This validates that the endurance test induces muscle fatigue both among healthy individuals and individuals with pain.

We also included a general fitness training group who performed leg cycling while relaxing the shoulders. Previous research in other populations has shown physiological adaptations in sites distant from the trained muscles [30, 31]. Increased blood flow to the forearms [32] and nonworking limb [33] has also been shown in response to leg exercise. Our hypothesis was that both specific strength training and general fitness training would improve muscle function compared with the reference intervention. However, in the present study leg cycling did not improve muscle fiber capillarization or muscle endurance of the trapezius muscle. Thus, of the three present interventions specific strength training remains the most effective for improving muscle function in women with trapezius myalgia.

In conclusion, the case-control study showed that women with trapezius myalgia have lower strength-endurance capacity during repetitive maximal contractions of the trapezius muscle compared with healthy controls, along with lower muscle activity (EMG amplitude). Moreover, relaxation of force—measured as the rate of force relaxation—occurred more slowly in women with trapezius myalgia, although the ability to fully relax the muscles between contractions was not lower than that in healthy controls. Moreover, the intervention study demonstrated that high-intensity strength

training effectively improves strength capacity during repetitive contractions of the painful trapezius muscle attaining functional levels comparable to the healthy control group together with their decrease in pain. This finding was accompanied with muscle fiber hypertrophy and increased capillarization per muscle fiber, which may at least partly explain the functional improvements. By contrast, leg cycling did not improve trapezius muscle function. Collectively, the present findings emphasize the importance of implementing specific resistance exercises in rehabilitation programmes for adults with trapezius myalgia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Effect of Brief Daily Resistance Training on Occupational Neck/Shoulder Muscle Activity in Office Workers with Chronic Pain: Randomized Controlled Trial

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Purpose. This study investigates the acute and longitudinal effects of resistance training on occupational muscle activity in office workers with chronic pain. **Methods.** 30 female office workers with chronic neck and shoulder pain participated for 10 weeks in high-intensity elastic resistance training for 2 minutes per day ($n = 15$) or in control receiving weekly email-based information on general health ($n = 15$). Electromyography (EMG) from the splenius and upper trapezius was recorded during a normal workday. **Results.** Adherence to training and control interventions were 86% and 89%, respectively. Compared with control, training increased isometric muscle strength 6% ($P < 0.05$) and decreased neck/shoulder pain intensity by 40% ($P < 0.01$). The frequency of periods with complete motor unit relaxation (EMG gaps) decreased acutely in the hours after training. By contrast, at 10-week follow-up, training increased average duration of EMG gaps by 71%, EMG gap frequency by 296% and percentage time below 0.5%, and 1.0% EMGmax by 578% and 242%, respectively, during the workday in m. splenius. **Conclusion.** While resistance training acutely generates a more tense muscle activity pattern, the longitudinal changes are beneficial in terms of longer and more frequent periods of complete muscular relaxation and reduced pain.

1. Introduction

Since the start of the industrial revolution in the middle of the 19th century, there have been huge social upheaval and massive technological advances, majorly impacting our way of life. This encompasses a more sedentary working life with extensive computer use [1], illustrated by the fact that as much as 41% of European workers use computer for at least a quarter of the working day [2]. This increases the time with static body postures and repetitive movements of the arm, shoulder, and hand, which has been associated with development of musculoskeletal disorders [3, 4]. Concurrently with this

tendency, there has been a pronounced increase in the number of computer-related muscular complaints especially in the neck/shoulders [5], and it has been reported that more than 50% of workers using computer at least 15 hours per week develop muscular skeletal symptoms in the upper extremities within their first work year [6]. This has great individual and societal consequences as neck/shoulder pain in white-collar workers has been shown to increase the risk for long-term sickness absence by 35% [7].

Systematic reviews of prospective cohort studies show that gender (woman) and a prior history of neck pain are the strongest predictors for development of neck pain in

computer workers [8]. Gender differences may be due to differences in work tasks, work techniques, and women doing more stereotype work tasks relative to men, but also the fact that women in a broad sense at a given work load would have a greater relative exposure due to lower muscle strength [9–12]. Surprisingly, a recent systematic review showed limited or conflicting evidence for work-related physical and psychosocial factors such as duration of computer and mouse use, influence at work, and job demands [8]. However, such epidemiological studies are often based on questionnaires or software-based registrations of computer use but lack physiological measurements, for example, muscle activity patterns.

Tension or activity of the neck/shoulder muscles may play an important role in the development of neck/shoulder pain and can be measured with electromyography during work. The type of activity patterns in the neck/shoulders muscles associated with computer work causes a selective activation of low-threshold motor units with type I muscle fibers. This causes both reduced local blood flow and an accumulation of calcium (Ca^{2+}), which can lead to musculoskeletal pain [13, 14]. Previous studies have shown an association between higher trapezius muscle activity and neck/shoulder pain [15, 16]. In particular, the frequency of gaps in trapezius muscle activity, that is, periods with complete motor unit relaxation, seems to be associated with neck/shoulder pain [17, 18]. A recent study has documented a longitudinal association between occupational neck/shoulder muscle activity and the risk for developing pain [19]. Thus, individuals with higher levels of occupational neck/shoulder muscle activity, that is, higher levels of muscle tension, may be at higher risk of developing neck pain. Consequently, interventions to induce a more relaxed muscle activity pattern during work may be beneficial.

Previous research has shown that physical exercise reduces musculoskeletal pain [20–22]. Some studies have investigated the effect of resistance training on neck/shoulder pain. While an acute increase in pain can occur in response to a single bout of high-intensity resistance training at the beginning of the training period in neck pain patients [23], previous studies have shown beneficial long-term effects of resistance training in terms of reduced neck pain [24–26]. Our lab has previously shown that office workers and laboratory technicians experience promising and effective reductions in neck/shoulder/arm pain in response to 10–20 weeks of resistance training with either dumbbells or elastic resistance bands [27–29], and a dose-response analysis indicated that one to two 20 minute training sessions per week appear to be sufficient for pain relief [30]. Importantly, a moderate reduction in pain [28] and muscle tenderness [27] can be obtained in response to as little as two minutes of daily neck/shoulder resistance training performed as a single set to failure. However, the mechanisms of pain reduction in response to such minimal amounts of high-intensity training are unknown. It can be speculated that resistance training causes reductions in the relative muscle force used or altered muscle recruitment patterns during work.

This study investigates the effect of brief daily resistance training on the acute and longitudinal changes in occupational electromyographic activity of the neck muscles (m. splenius and m. trapezius) in female office workers with neck/shoulder pain. We hypothesized that performing two minutes of daily neck/shoulder resistance training for 10 weeks will beneficially alter the muscular activity pattern and thereby reduce neck/shoulder pain. In detail, we hypothesized that the training group will experience (i) an enhanced frequency of EMG gaps, (ii) a prolonged duration of the EMG gaps, and (iii) have a larger percentage of time with a minimal muscular activity compared with the control group.

2. Methods

2.1. Study Design and Participants. This study is nested in a larger randomized controlled trial performed in Copenhagen, Denmark. In the larger parallel-group single-blind randomized controlled trial, the participants were allocated to training groups of two or twelve minutes of daily resistance training or to a control group. For the present analyses, we were particularly interested in the mechanisms of pain reduction in the group performing a single set to failure and included a subsample of 2×15 participants. In the larger study, 198 office workers with frequent neck/shoulder pain, but without traumatic injuries or serious chronic disease participated. However, due to the time-consuming procedure of performing full-day EMG measurements, it was not possible in the present study to perform daily EMG measurements on all 198 participants. The detailed procedure of recruitment and concealed randomization of the 198 participants is described elsewhere [28]. In brief, the participants recruited were employees from one large office workplace characterized by computer use for the majority (90%) of the working time. Figure 1 provides an overview of the entire flow of the participants throughout the study. After randomisation, emails were sent to the participants of the larger study inviting them to participate in workday measurements with EMG. When 15 positive replies in each group were obtained, the recruitment was closed. The minimal sample size was estimated on background of data from a prior study on EMG measurements [31]. The recruitment was started during August 2009 and was terminated in September 2009, where the baseline measurements were also conducted. The last participant had follow-up in December 2009.

The outcomes in this nested study of the trial were change in (i) frequency of EMG gaps under 0.5% EMGmax (number per minute), (ii) duration per EMG gap under 0.5% EMGmax (length in seconds), and (iii) time spent under 0.5% EMGmax (percentage distribution). On an exploratory basis, the time spent under 1.0%, 1.5%, and 2.0% EMGmax was also investigated. These outcomes were assessed both acutely after a training session and longitudinally following the 10-week intervention. There were no changes made to either methods or study protocol after trial registration.

All participants were informed about the purpose and content of the study and gave their written informed consent prior to participating in the study, which conformed

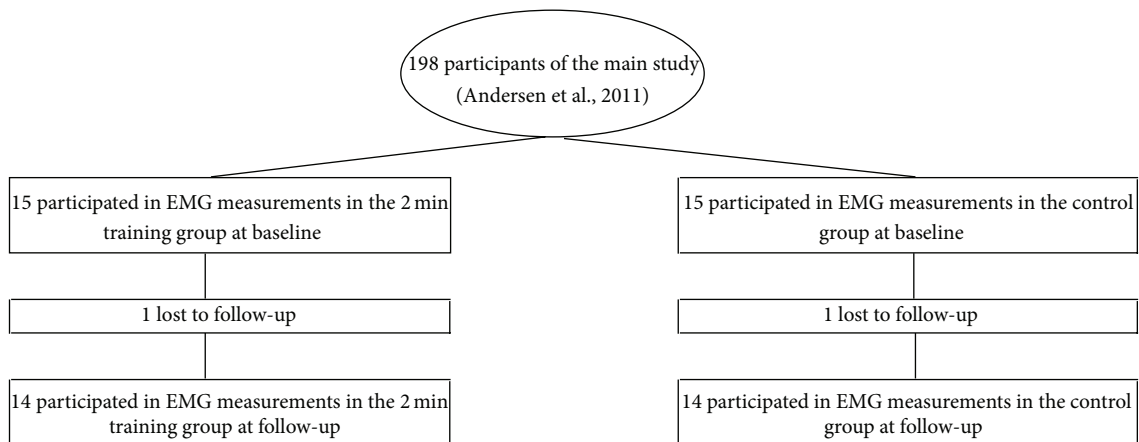


FIGURE 1: Flow chart.

to The Declaration of Helsinki and was approved by the local ethical committee of Copenhagen and Frederiksberg (HC2008103).

2.2. Intervention. The intervention has been described in detail elsewhere [28]. In brief, the training group of the present study performed two minutes of shoulder abductions in the scapular plane with an elastic tubing (Thera-Band) as added resistance on a daily basis on workdays during their working hours. This exercise is also known as “lateral raise” and it effectively targets most neck/shoulder muscles [31, 32]. Participants performed a single set of exercise with as many consecutive repetitions as possible to momentary muscular fatigue (i.e., to failure) for a maximum duration of two minutes. Afterwards, they registered all training activities in a log to allow for a gradual progression in repetitions and resistance. The control group received e-mail-based information once a week during the 10-week intervention period on various aspects of general health (e.g., diet, smoking, alcohol, physical exercise, stress management, workplace ergonomics, and indoor climate).

2.3. Adherence. The adherence in both groups was monitored by weekly internet-based questionnaires. Adherence for the training group was defined as the number of completed training session expressed as a percentage of the total number of training sessions throughout the intervention period. The adherence for the control group was defined as the number of read informational emails expressed as a percentage of the total number of informational emails throughout the intervention period.

2.4. Experimental Setup. The EMG signal was recorded from m. trapezius and m. splenius of the dominant side. The recordings were collected using a bipolar surface EMG configuration (Ambu Blue Sensor N, N-00-S, Ambu A/S, Ballerup, Denmark) using an interelectrode distance of two cm [33, 34]. Prior to applying the electrode pairs, the skin was abraded to ensure an impedance level less than 10 kΩ.

The electrode pairs were placed in accordance with the SENIAM guidelines (<http://www.seniam.org/>).

Each pair of EMG electrodes was connected to a wireless probe (Velamed Medizintechnik GmbH) connected to the skin, serving as reference electrode. Furthermore, the probe preamplified the EMG signal (gain 400) before transmitting the data to 16-channel 16 bit PC-interface receiver in real-time (Noraxon Telemetry DTS Telemetry, Noraxon, AZ, USA). All data were collected using a sample rate of 1500 Hz within a bandwidth of 10–500 Hz. This wireless EMG-system has shown to be valid and reliable for collecting EMG-data from the neck/shoulder musculature [35, 36] as well as other muscular groups [37–39].

2.5. Experimental Procedure. All EMG recordings were performed during normal working hours while the participants performed their usual work. To obtain resting EMG at the beginning of the workday, participants performed 30 seconds of instructed seated rest with closed eyes and complete arm support while focusing on completely relaxing the shoulder and neck muscles. This was followed by the three reference tasks performed in accordance with outlined guidelines [40]. While seated, the participants held their arms straight and horizontal in 90 degree abduction, the hands were relaxed and palms faced downwards with no additional weight added for a period of 20 seconds [18, 41]. After conducting the reference tasks, the participants were instructed to perform their usual work. After a period of between 60 to 90 minutes the participants conducted an identical reference task. Hereafter, the control group resumed their normal work, while the training group performed their daily training session consisting of two minutes elastic resistance training before resuming their normal work.

After another period of between 60 to 90 minutes just before terminating the measurement, the participants again conducted the reference task. This was followed by a resisted maximal voluntary contraction to obtain maximal EMG for normalization of the obtained EMG signals. The maximal contraction was conducted in the position of the reference tasks with the only addition of an opposing force provided by

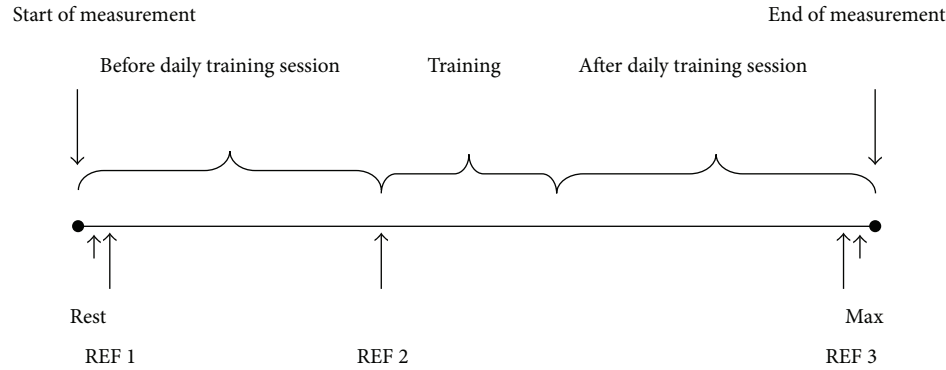


FIGURE 2: A schematic overview of the measurement period. Rest is equivalent to the resting period where the resting EMG amplitude was determined, REF is equivalent to the three reference tasks, and Max corresponds to the time of the maximal contraction.

TABLE 1: Baseline characteristics, Mean \pm SD. No significant differences were observed.

	Training (N = 15)	Control (N = 15)
Age (years)	41.7 \pm 10.8	40.5 \pm 7.27
Height (cm)	168.8 \pm 6.68	166.1 \pm 4.44
Weight (kg)	66.5 \pm 9.07	65.2 \pm 10.1
BMI (kg·m ²)	23.3 \pm 2.87	23.6 \pm 3.58
Pain intensity previous 3 weeks (Scale 0–10)	3.44 \pm 1.40	3.24 \pm 1.37
Systolic BP (mmHg)	125 \pm 12.3	127 \pm 15.2
Diastolic BP (mmHg)	86 \pm 8.37	84 \pm 9.22
Isometric muscle strength (Nm)	41.1 \pm 6.71	37.6 \pm 13.21
Computer use (% work time)	98.4 \pm 6.25	95.0 \pm 10.4
Weekly working time (hours)	38.2 \pm 3.9	37.0 \pm 3.47
Duration of office work (Years)	10.3 \pm 8.6	11.7 \pm 8.9

the test instructor. The participants then performed isometric maximal voluntary contractions two times for five seconds separated by rest periods of 30 seconds. For an overview of the sampling protocol see Figure 2.

2.6. Data Collection Area and Recording Time. In the baseline screening questionnaire, the participants reported that they spend the vast majority of their working hours doing computer work, see Table 1. Therefore, prior to each measurement, a data collection area was defined which only included the nearest area around the primary workstation of the participant. This would cause the EMG probes to stop recording data when the participants were not present in the predefined data collection area and thereby automatically filtering out periods where the employees performed other types of activities than their main job function, see Table 2.

2.7. Processing of Data. All data processing was performed in MatLab (MathWorks, version 7.5.0 342, R2007b). The first step in the data processing was to filter out the periods of work time where the participants were outside the predefined data collection area. In the measurements, this was visualized as

a completely flat line without fluctuations of EMG amplitude, and the program therefore removed periods which assumed identical values over a period of minimum 100 ms.

There were no statistical differences regarding the total recording time and the computer work time between the two groups, see Table 2. For a detailed overview of the relationship between total recording time and the effective time that the participants were located within the predefined data collection area, see the EMG signal which was normalized by determining the maximal Root Mean Square (RMS) during the isometric maximal voluntary contraction. RMS was determined using a moving window with a width of 1500 data points (i.e., 1 sec) and a movement of 100 ms [42]. Subsequently, the resting EMG amplitude was determined, by identifying the lowest RMS within a time period of five seconds during the resting period. The lowest RMS value was quadratically subtracted from all other EMG signals [43]. Hereafter, the RMS plots for both the maximal contraction and the relaxation measurement were visually controlled for 50 Hz interference, unilateral spikes, and abnormalities in the EMG signal.

Finally, the RMS for the working periods before (first 60–90 minutes of data sampling) and after the daily training session (last 60–90 minutes) was determined, using the same procedure as described above. This allowed the identification of periods where the EMG amplitude was below a predefined percentage of the normalized EMGmax, which was termed an EMGgap. In this study, the following percentages of the normalized EMGmax had a particular interest: 0.5%, 1.0%, 1.5%, and 2% EMGmax. According to previous studies, 0.5% EMGmax represents the boundary for total relaxation of a motor unit, whereas the remaining values represent different degrees of activation of the smallest motor units [41]. However, all periods with a very low level of muscle activity up to 2% of maximal EMG had a particular interest. In order to be classified as an EMGgap, the EMG amplitude additionally had to be below 0.5% EMGmax for a period of at least 0.2 s [44, 45].

2.8. Statistical Analysis. All statistical analyses were performed in SAS statistical software (SAS version 9.2, SAS Institute, Cary, NC) and were performed in accordance with

TABLE 2: Recording time corresponding to the average number of total minutes recorded. Effective recording time corresponding to the percentage time where the participants were present in the predefined data collection area, that is, percentage of the total minutes recorded included in the data analysis, median (interquartile range). No significant differences were observed.

		Training (N = 15)	Control (N = 15)
Recording time (min)			
Before daily training session	Week 0	60.0 (42.0–69.1)	64.5 (49.8–79.2)
	Week 10	72.1 (65.3–77.4)	75.5 (56.8–87.8)
After daily training session	Week 0	82.7 (70.1–96.2)	60.9 (47.9–74.4)
	Week 10	62.3 (39.6–82.6)	59.7 (46.7–73.2)
Effective recording time (%)			
Before daily training session	Week 0	79.7 (70.8–92.9)	84.2 (71.9–95.1)
	Week 10	89.3 (84.3–92.5)	93.6 (40.9–97.3)
After daily training session	Week 0	92.2 (73.4–97.0)	93.3 (87.9–95.1)
	Week 10	93.7 (85.6–98.5)	94.3 (73.5–97.1)

the intention-to-treat principle by including data from all available participants regardless of actual adherence [46]. Muscle strength and pain were analysed using parametric statistics and reported as mean (SD). However, a Shapiro-Wilk test showed that EMG data generally did not fit a normal distribution. Therefore, we used nonparametric statistics, Mann-Whitney *U* test, to determine between-group differences in all EMG parameters and reported data as medians (interquartile range). All comparisons were performed two-tailed and a probability level of $P < 0.05$ was considered to indicate significant differences.

3. Results

Table 1 gives an overview of the characteristics in the two intervention groups at baseline and shows that the groups were matched for demographic, clinical, and work related characteristics.

During the intervention period, the training group performed an average of 4.3 of the 5 scheduled training sessions per week, which is equivalent to an 86.8% training adherence, while the control group had read on average 8.9 of the 10 informational emails corresponding to an adherence of 89%.

Overall, two participants were lost to follow-up, one participant in each intervention group, both due to lack of time. No adverse events were reported during the intervention or EMG measurements.

3.1. Recording Time. Table 2 displays the relationship between the total recording time and the effective time the participants were located within the predefined data collection area. As shown in the table, there was no difference in the total sampling time between the intervention groups at either week 0 or week 10. Furthermore, there were no differences within each intervention group at either week 0 or week 10.

3.2. Acute Effect of Training. Table 3 shows the frequency of EMG gaps (number per minute). The training group significantly decreased the frequency of EMG gaps in m. splenius by almost 35% from 12.3 to 8.0 gaps/minute acutely in response to the training session at follow-up ($P < 0.05$), that is, an acute worsening of the muscle activity pattern.

3.3. Effect of the 10-Week Intervention. Table 3 shows the frequency of EMG gaps. Compared with the control group, the training group significantly increased the number of EMG gaps after 10 weeks of training in m. splenius by approximately 300% from 3.1 to 12.3 gaps/minute ($P < 0.05$), that is, a more relaxed muscle activity pattern.

Table 4 shows baseline and follow-up values for pain intensity and muscular strength for both intervention groups. After the intervention period, the training group significantly decreased neck/shoulder pain intensity by 40% compared with the control group ($P < 0.01$). Furthermore, the training group improved muscular strength by 6%, which was significant compared with the control group ($P < 0.05$).

Tables 5(a) and 5(b) show the percentage distribution of time spent under different levels of EMGmax for m. trapezius and m. splenius, respectively. After 10 weeks of training, there were a significant increase in the percentage of time spent under both 0.5% ($P < 0.01$) and 1.0% ($P < 0.05$) EMGmax in m. splenius for the training group when compared with the control group, from 2.3% to 15.6% and from 7.6% to 26.0%, respectively, corresponding to a 575% and 242% increase in time.

Table 6 shows the average duration in seconds per EMG gap. Compared with the control group, there was a significant increase in the average duration per gap in both m. trapezius and m. splenius for the training group after 10 weeks of training ($P < 0.05$ and $P < 0.01$, resp.) from 0.72 sec to 1.26 sec and from 0.42 sec to 0.72 sec, respectively, corresponding to a 75% and 71% increase, that is, longer periods with complete relaxation.

3.4. Reference Contraction. There was no change in the average EMG amplitude during the reference contraction (i.e., arms 90 degree abducted) from before to after the daily training session, showing that the EMG measurements were stable throughout the day.

4. Discussion

The main finding of the present study was the change in occupational neck muscle activity in response to brief daily resistance training. These alterations were shown both

TABLE 3: Frequency of EMG gaps (periods per minute below 0.5% EMGmax) for m. trapezius and m. splenius, median (interquartile range).

		Training (N = 15)	Control (N = 15)
Trapezius			
Before daily training session	Week 0	8.5 (4.4–11.6)	4.2 (1.9–11.5)
	Week 10	8.2 (6.3–15.3)	3.7 (1.1–13.2)
After daily training session	Week 0	7.4 (5.4–11.7)	3.0 (2.0–12.2)
	Week 10	7.6 (4.4–15.2)	2.2 (1.2–6.4)
Splenius			
Before daily training session	Week 0	3.1 (1.4–10.9)	5.0 (1.6–10.9)
	Week 10	12.3 (4.8–15.2) ^b	1.1 (0.5–5.8)
After daily training session	Week 0	5.0 (2.7–7.8)	3.1 (1.3–11.7)
	Week 10	8.0 (3.5–14.5) ^d	1.3 (0.5–6.5)

^bP < 0.05 significant change from baseline to follow-up in the training group compared with the control group. ^dP < 0.05 significant change from before to after the daily training session.

TABLE 4: Pain intensity and muscular strength at week 0 and week 10, Mean ± SD.

		Training (N = 15)	Control (N = 15)
Pain intensity (scale 0–10)	Week 0	3.44 ± 1.40	3.24 ± 1.37
	Week 10	2.04 ± 1.60 ^a	3.45 ± 1.99
Isometric muscle strength (Nm)	Week 0	41.1 ± 1.7	37.6 ± 3.4
	Week 10	43.2 ± 1.3 ^b	36.5 ± 3.3

^aP < 0.01 significant change from baseline to follow-up in the training group compared with the control group. ^bP < 0.05 significant change from baseline to follow-up in the training group compared with the control group.

acutely in response to a single training session and longitudinally following the 10 week intervention—however with opposite impact on the muscle activity pattern. While the single training session acutely altered the muscle activity pattern so that less frequent periods of muscular relaxation were observed, the longitudinal change in muscle activity led to both longer and more frequent periods of complete muscular relaxation. The longitudinal changes were observed concurrently with increased muscle strength and reduced pain of the neck muscles.

4.1. Acute Worsening. The frequency of EMG gaps decreased immediately after the training session in the splenius muscle, which may lead to increased muscle tension and perceived discomfort. Although we did not measure acute changes in pain in the present study, previous research has reported an acute increase in muscular pain immediately after high-intensity resistance training in women with trapezius myalgia [23]. However, in that study, the acute aggravation of muscular pain disappeared within two hours and the participants experienced an overall pain reduction following a 10-week training period [23]. Our study suggests that the previously observed acute aggravation of pain may be related to the acute increase in muscle tension immediately after resistance training. These results also highlight the importance of

explaining to patients that their pain may acutely worsen in response to high-intensity resistance training, but improve in the long term. This may have important practical implications for adherence to the training program. As an alternative explanation of the present findings, EMG amplitude may be artificially increased immediately after training due to increased blood flow. That is, increased blood flow results in an accumulation of liquids and electrolytes in the active muscles, which may improve the conductivity of the electrical signal and thereby increase the EMG amplitude without an actual increase in muscle tension. A possible reason for this phenomenon to only have an impact after the intervention period may primarily be due to the higher intensity by which the resistance training was performed, leading to higher postexercise hyperemia.

4.2. Longitudinal Improvement. The 10-week training period led to decreased pain and increased muscular strength in the neck/shoulder muscles. This is in accordance with the main study including all 198 participants [28]. As a possible explanatory mechanism for the observed pain reduction, we found a number of potentially beneficial changes in neck muscle activity. Previous studies have shown that sustained muscular activity in trapezius muscle is a risk factor for developing neck pain [15, 19]. Furthermore, former studies have shown that muscular activity less than 0.5% EMGmax represents total muscular relaxation and less than 2.0% EMGmax represents sole activation of the smallest motor units [41]. Henneman's size principle and the Cinderella Hypothesis state that the motor units with the lowest threshold will create the majority of muscle tension during sustained low intensity work tasks [47, 48]. Thus, the same motor units will remain active throughout the workday regardless of a reduced relative work strain and increased muscular strength. Therefore, the threshold of 0.5% EMGmax—representing complete muscular relaxation—is relevant when trying to avoid prolonged strain of the smallest motor units.

Our study showed increased frequency of EMG gaps, that is, periods with complete muscular relaxation, defined as muscular activity below 0.5% EMGmax, following 10 weeks of resistance training. This more relaxed activity pattern in

TABLE 5: (a) Percentage time spent under given % EMGmax for m. trapezius, median (interquartile range). (b) Percentage time spent under given % EMGmax for m. splenius, median (interquartile range).

(a)			Training (N = 15)	Control (N = 15)
Trapezius	0.5% EMGmax			
	Before daily training session	Week 0	18.5% (5.1–39.1)	11.4% (4.3–17.6)
		Week 10	24.0% (16.0–34.6)	4.1% (0.9–27.8)
	After daily training session	Week 0	15.1% (11.1–30.2)	9.8% (3.1–12.7)
		Week 10	25.8% (13.4–42.2)	4.9% (1.5–7.9)
	1.0% EMGmax			
	Before daily training session	Week 0	39.0% (14.1–50.8)	21.3% (7.6–34.1)
		Week 10	32.3% (24.3–54.8)	9.9% (2.9–35.5)
	After daily training session	Week 0	25.9% (21.2–41.2)	12.6% (6.3–26.0)
		Week 10	37.0% (20.7–54.3)	6.6% (3.9–13.9)
	1.5% EMGmax			
	Before daily training session	Week 0	47.3% (24.3–57.3)	28.3% (10.2–43.9)
		Week 10	38.6% (32.3–66.1)	19.5% (5.1–40.4)
	After daily training session	Week 0	36.1% (29.1–50.6)	15.2% (10.5–33.3)
		Week 10	46.2% (26.5–62.8)	11.0% (5.7–18.8)
	2.0% EMGmax			
Before daily training session	Week 0	55.0% (37.6–61.9)	34.7% (15.6–52.3)	
	Week 10	44.5% (39.2–72.9)	27.9% (7.3–47.7)	
After daily training session	Week 0	44.9% (35.8–58.3)	19.5% (14.2–39.4)	
	Week 10	53.6% (32.9–74.7)	14.4% (7.8–28.5)	
(b)			Training (N = 15)	Control (N = 15)
Splenius	0.5% EMGmax			
	Before daily training session	Week 0	2.3% (1.0–20.7)	7.1% (3.8–11.1)
		Week 10	15.6% (11.7–28.5) ^a	0.8% (0.2–4.6)
	After daily training session	Week 0	5.0% (2.2–8.9)	4.1% (1.3–10.4)
		Week 10	14.3% (8.5–20.0)	1.9% (0.3–5.9)
	1.0% EMGmax			
	Before daily training session	Week 0	7.6% (5.8–35.1)	11.1% (6.4–24.7)
		Week 10	26.0% (21.9–45.0) ^b	3.5% (1.4–12.6)
	After daily training session	Week 0	11.9% (4.3–19.4)	5.9% (2.0–22.5)
		Week 10	23.9% (12.3–29.8)	3.7% (1.0–12.4)
	1.5% EMGmax			
	Before daily training session	Week 0	18.2% (11.1–48.5)	21.0% (7.6–29.8)
		Week 10	37.2% (29.8–55.4)	7.3% (2.8–20.8)
	After daily training session	Week 0	24.6% (10.1–37.6)	8.2% (4.6–32.5)
		Week 10	34.2% (19.2–40.8)	5.7% (2.5–18.8)
	2.0% EMGmax			
Before daily training session	Week 0	30.1% (19.8–57.9)	31.0% (10.7–37.8)	
	Week 10	46.0% (36.2–62.6)	10.6% (5.4–29.3)	
After daily training session	Week 0	35.1% (19.9–51.2)	11.9% (8.8–35.5)	
	Week 10	41.0% (29.8–52.8)	9.7% (4.3–26.5)	

^aP < 0.01 significant change from baseline to follow-up in the training group compared with the control group. ^bP < 0.05 significant change from baseline to follow-up in the training group compared with the control group.

TABLE 6: Duration of each EMG gap (seconds) under 0.5% EMGmax for m. trapezius and m. splenius, median (interquartile range).

		Training (N = 15)	Control (N = 15)
Trapezius			
Before daily training session	Week 0	0.72 (0.6–1.74)	0.9 (0.54–1.68)
	Week 10	1.26 (0.6–1.98) ^b	0.6 (0.42–1.02)
After daily training session	Week 0	1.08 (0.66–1.8)	0.96 (0.6–1.38)
	Week 10	1.56 (0.72–2.76)	0.78 (0.36–1.26)
Splenius			
Before daily training session	Week 0	0.42 (0.36–0.48)	0.6 (0.48–0.96)
	Week 10	0.72 (0.54–0.78) ^a	0.36 (0.3–0.48)
After daily training session	Week 0	0.54 (0.42–0.6)	0.54 (0.42–0.72)
	Week 10	0.72 (0.54–1.02)	0.48 (0.42–0.54)

^a $P < 0.01$ significant change from baseline to follow-up in the training group compared with the control group. ^b $P < 0.05$ significant change from baseline to follow-up in the training group compared with the control group.

the neck muscles is likely to reduce fatigue and pain. Additionally, increased duration of EMG gaps in both m. splenius and m. trapezius was found. Prolonged duration of EMG gaps leads to longer episodes of complete muscular relaxation, which potentially can reduce the pain in the neck/shoulder muscles. A possible explanation for this relationship between the length of the EMG gap and the level of pain intensity can be that shorter EMG gaps, compared to longer EMG gaps, cause a higher average work strain [49]. In addition, previous research has found a positive association between pain in the neck/shoulder muscles and EMG gap length [18, 50]. The study by Blangsted showed that pain free subjects experienced EMG gaps of longer duration compared with subjects who suffered from neck/shoulder pain [50]. Furthermore, increased muscular activity in m. trapezius has been linked to trapezius myalgia [16]. Altogether, these studies support the potential effect of the prolonged and more frequent EMG gaps as a possible explanatory mechanism for the reduced neck/shoulder pain observed in the present study.

Rosendal and coworkers have shown that women suffering from chronic neck muscle pain experience increased levels of both lactate and pyruvate in the interstitium as a result of low-force repetitive work [51, 52]. This has been suggested to be a reflect increased anaerobic metabolism related to a reduced blood flow as a consequence of an insufficient capillarization of the muscle fibres. This is supported by findings showing impaired blood flow to the active muscles in people suffering from myalgia [53, 54]. In the present study, the underlying physiological explanation between increased frequency and duration of EMG gaps and decrease of neck pain may partly be due to enhanced blood flow and thereby increased oxygenation and less anaerobic metabolism due to better muscular relaxation. In a previous study, Kadi and coworkers reported enhanced blood flow as result of an improved capillarization with corresponding decrease in muscular pain after a period of specific resistance training [55]. Thus, as another explanation for the present findings, participants in the training group may have experienced a combination of greater improved capillarization combined with a more relaxed muscle pattern, which together allows for enhanced blood flow and thereby oxygen to the active muscles.

In general, the findings of the present study suggest that the splenius muscle compared with trapezius is the primary site for pain sensation in the neck/shoulder muscles due to the fact that EMG alterations primarily appear in the splenius. This is supported by findings of a higher prevalence of severe tenderness in the neck extensors compared with trapezius [56]. This could have practical implication when treating people who suffer from pain in the neck/shoulder muscles, including trapezius myalgia, by having a greater focus on the state of the neck extensors and not only the trapezius muscle. However, more research is needed to determine whether pain in the neck/shoulders is related more strongly to the splenius than the trapezius.

4.3. Limitations. A limitation to the present study is that participants could not be blinded due to the general design with a designated training group. This introduces multiple risks of nonspecific effects including possible placebo effects in respect to changes in perceived pain [57, 58] as well as the possibility of a Hawthorne effect [59]. However, it should be noted that the testers, besides the second reference measurement, only interacted with the participants at initiation and termination of the measurements and therefore had no contact with the participants during the time of the measurements, which likely minimize any possible Hawthorne effect. Furthermore, the present study used objective measures of muscle activity during the working day, minimizing both the potential for placebo and Hawthorn effects to act on EMG measurements. Thus, if the muscle activity pattern did change over time, it is unlikely that this is caused by the participants not being blinded to the intervention.

The relatively small sample size increases the risk for statistical type II errors, that is, not finding a significant difference when there is in fact a difference. On the other hand, the lack of Bonferroni correction will increase the risk for statistical type I errors. However, performing a Bonferroni correction will increase the risk of type II errors [60]. On this background, the Bonferroni correction is often considered as being rather conservative and the decision whether to use a Bonferroni correction or not is therefore a matter of balancing the pros and cons. Bonferroni corrections are appropriate when outcome measures are completely random,

for example, throwing a dice. However, as this study had pre-defined hypotheses, the use of Bonferroni correction appears inappropriate.

The use of surface EMG to determine the muscular activity patterns is sensitive to a number of different parameters including electrode placement [61, 62] and the interelectrode distance [63]. Furthermore, crosstalk from the surrounding musculature has a potential to impact on the EMG [64, 65]. However, this should not affect the interpretation of the findings due to the use of recommended procedures when performing surface EMG [66] as well as prior literature has shown that it is possible to differentiate the EMG signal from m. splenius and m. trapezius [67].

5. Conclusion

The primary objective of this study was to investigate whether a brief daily resistance training session would have an effect on the muscular activity pattern of the neck/shoulder muscles. In respect to our hypothesis, we reported beneficial long-term changes in both the frequency and duration of the EMG gaps alongside with alterations in the time with minimal muscular activation. In summary, the acute response to a single session of resistance training appeared to generate an unfavourable muscle activity pattern. By contrast, the longitudinal changes were beneficial in terms of longer and more frequent periods of complete muscular relaxation and reduced pain; however, these findings were more pronounced in m. splenius compared to m. trapezius. Future studies on neck/shoulder pain should consider focusing also on the splenius rather than the trapezius alone.

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Clinical Study

The Effect of NeuroMuscular Electrical Stimulation on Quadriceps Strength and Knee Function in Professional Soccer Players: Return to Sport after ACL Reconstruction

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The aim of this study was to assess the clinical efficacy and safety of NMES program applied in male soccer players (after ACL reconstruction) on the quadriceps muscle. The 80 participants (NMES = 40, control = 40) received an exercise program, including three sessions weekly. The individuals in NMES group additionally received neuromuscular electrical stimulation procedures on both right and left quadriceps (biphasic symmetric rectangular pulses, frequency of impulses: 2500 Hz, and train of pulses frequency: 50 Hz) three times daily (3 hours of break between treatments), 3 days a week, for one month. The tensometry, muscle circumference, and goniometry pendulum test (follow-up after 1 and 3 months) were applied. The results of this study show that NMES (in presented parameters in experiment) is useful for strengthening the quadriceps muscle in soccer athletes. There is an evidence of the benefit of the NMES in restoring quadriceps muscle mass and strength of soccer players. In our study the neuromuscular electrical stimulation appeared to be safe for biomechanics of knee joint. The pathological changes in knee function were not observed. This trial is registered with Australian and New Zealand Clinical Trials Registry ACTRN12613001168741.

1. Introduction

One key goal of successful anterior cruciate ligament (ACL) reconstruction is return to sports. Athletes who sustain ACL tears require successful reconstruction in order to continue participating in cutting and pivoting sports. The two most commonly reported treatment options for ACL injuries in sport is surgical operation and physical therapy management [1].

Quadriceps muscle weakness after anterior cruciate ligament (ACL) reconstruction is a serious problem, but the

mechanisms underlying these chronic strength deficits are not clear. For example, Krishnan and Williams [2] examined quadriceps strength in people 2–15 years after ACL reconstruction and tested the hypothesis that chronic quadriceps weakness is related to levels of voluntary quadriceps muscle activation, antagonistic hamstrings moment, and peripheral changes in muscle. Knee extensor strength and activation were evaluated in 15 ACL reconstructed and 15 matched uninjured control subjects using an interpolated triplet technique. Electrically evoked contractile properties were used to evaluate peripheral adaptations in the quadriceps muscle.

Antagonistic hamstrings moments were predicted using a practical mathematical model. Knee extensor strength and evoked torque at rest were significantly lower in the reconstructed legs ($P < 0.05$). Voluntary activation and antagonistic hamstrings activity were similar across legs and between groups ($P > 0.05$). Regression analyzes indicated that side-to-side differences in evoked torque at rest explained 71% of the knee extensor strength differences by side ($P < 0.001$).

Adams et al. [3] noticed that quadriceps strength deficit is significant after ACL injury, ranging from 15% to 40% (followup was obtained 502 patients at a mean of 14.1 years postoperatively). Regression analysis showed that the most statistically significant factor related to lower subjective scores was lack of normal knee extension and loss of normal flexion.

Neuromuscular electrical stimulation (NMES) is the application of electrical current to elicit a muscle contraction and seems to be helpful for strengthening the muscles. Use of NMES for orthopedic and neurologic rehabilitation has grown significantly in recent years and seems to be documented [1, 4–7].

The neurophysiologic principles on which the treatment is based have been studied in animal and human subjects. A nerve action potential may be elicited by a “command” originating in the motor cortex of the brain or by an electrically induced stimulus at the periphery. In either case, the mechanism of action potential propagation and release of synaptic transmitter substance is the same. A fundamental difference between the two mechanisms and the resultant muscle contraction exists in the recruitment order of individual motor units [7].

During a voluntary muscle contraction, smaller motor units composed primarily of type I (slow twitch fibers), fatigue-resistant fibers tend to be recruited first. Different motor units are recruited asynchronously. As some are relaxing, others are contracting and constant tension of the muscle is maintained. During electrical stimulation such as NMES (especially for 50–70 Hz frequencies), composed primarily of type II (fast twitch fibers), readily fatigable fibers are recruited first because their (larger diameter) motor nerves have low thresholds to electrical excitation [8, 9]. Motor units of similar thresholds lying superficially beneath the stimulating electrodes will be recruited simultaneously. As they begin to fatigue, tension in the muscle will begin to decrease unless the intensity of the stimulus is increased, recruiting additional motor units with higher thresholds or with similar thresholds, but more remote locations [9]. Excessive fatigue can be minimized during electrically induced muscle contraction by limiting the frequency at which the stimulus is applied and the duration of the contraction. Adequate rest periods between contractions will increase the likelihood that subsequent muscle contractions will be sufficiently strong. In the literature there are lots of theories (historical and modern) on mechanism of generating the action potential and muscle nerve conducting: electronic propagation, Hodgkin-Huxley theory, patch clamp technique, or theory of channel activation [9, 10].

The goal of improving human performance in sport and exercise has been an extremely interesting topic for coaches,

athletic trainers, physical therapists, exercise physiologists and athletes alike. Unfortunately, the utility of the NMES for sport application still remains controversial. For example, while many research studies find muscle strength and recovery after physical effort significantly improved by NMES [3, 4, 11–14], a few do not [8, 15, 16]. It is also unclear whether the NMES is completely safe. Some authors maintain that NMES could induce muscle damage or influence on function and biomechanics of the near articulations of the stimulated muscles [17].

Bax et al. [18] presented a systematic review and metaanalysis of randomized controlled trials to determine whether NMES is an effective modality for strength augmentation of the quadriceps femoris. A full content search for randomized controlled trials was performed in Medline, Embase, Cinahl, the Cochrane Controlled Trials Register, and the Physical Therapy Evidence Database. Only maximum volitional isometric or isokinetic muscle torque in Nm was used as main outcome measure and final conclusions are unclear. Authors stated that further research should be directed toward identifying the clinical impact at activity and participation levels and the optimal stimulation parameters of this modality. Well-prepared and documented, prospective, controlled studies are needed.

The objective of this study was to assess the efficacy and safety of NMES program applied in soccer players (after ACL reconstruction) on the quadriceps muscle. The primary study endpoint was a comparison of the change in muscle strength between the stimulated and control groups. The secondary end point was the analysis between groups of the change of quadriceps muscle circumference and other measured parameters as predictors of safety (whether there are any pathological changes in knee function) after NMES therapy.

2. Materials and Methods

All participants provided informed consent to this project that was approved by the Local Institutional Review Board of the Medical University of Silesia in Katowice, Poland. Trial is registered in Australian and New Zealand Clinical Trials Registry (ACTRN12613001168741).

2.1. Participants and Randomization. The 80 professional male soccer players (The Soccer Academy—ten soccer clubs from 2nd and 3rd Polish League) participated in experiments to measure the clinical effectiveness and safety of electrical stimulation. Participating subjects met the following inclusion criteria.

(1) They underwent arthroscopy surgery as follows: initially, an anteromedial incision was made on the proximal tibia and the gracilis and semitendinosus tendons were detached from their insertions on tibia. Subsequently, the tendons were removed to fashion the graft for ACL reconstruction. A tibial canal was established; through this canal, the femoral canal was created under arthroscopy guide. Finally, the graft was passed through the canals as a single bundle.

(2) They spent 6 months after operation.

(3) They received the same rehabilitation program before NMES procedures: week 1 (CPM Machine—start at 0–30 degrees and increase with not less than 10 degrees per day, PROM Wall Slides Seated Active Assistive Knee Flexion Prone Dangle Passive resting extension with heel prop Patellar Mobilizations, SLR x3 Flexion, Adduction, Abduction, Hamstring/Calf Stretches, Ankle Pumps, Gait Training, Home Exercise Program-2 or 3 times per day). Week 2–4 (Scar Mobilization/Massage, Proprioceptive Neuromuscular Facilitation, Progressive Resistive Exercises, Manual/Machine resisted leg press, Balance/Proprioception, Isometric Knee extension 90–60°, Stationary Bike, Minisquats progress up to 90°, Step ups, Retro Treadmill/Stairmaster, Hip abduction/external rotation) and week 4–16 (Functional Strengthening, Proprioceptive Neuromuscular Facilitation, Progressive Resistive Exercises, Manual/Machine resisted leg press, Balance/Proprioception, Squats to 90 degrees, Single leg squats, Step ups, Retro Treadmill/Stairmaster, and Review Home Exercise Program 2 times per day). Week 16–24 (Continue strength, endurance, proprioception progression, Begin double-leg hopping, jogging, and agility drills).

(4) They provided written informed consent to participate in the study.

Subjects with the following conditions were not allowed to participate or were excluded from the study:

- (1) women,
- (2) soccer practice for less than 3 years (share of the league for at least three years),
- (3) bone fracture in the last 2 years,
- (4) chronic sprain ankle,
- (5) a history of Achilles tendon injury.

Participants were randomly allocated to the groups. Computer-generated random numbers were sealed in sequentially numbered envelopes, and the group allocation was independent of the time and person delivering the treatment. The physician (research coordinator) who allocated the subjects to groups had 80 envelopes, each containing a piece of paper marked with either group A (NMES) or B (control). The physician would select and open an envelope in the presence of a physiotherapist to see the symbol and would then direct the patient to the corresponding group. Another physiotherapist collected the data and coded them into an Excel database. The “blinded” results were transferred to a Statistica version 10.0 database by a technician. The research coordinator had no contact with and could not identify the soccer players.

2.2. Procedures. All participants received an exercise program, including three sessions (Mondays, Wednesdays, and Fridays) weekly, for one month:

- (i) double-leg hopping, jogging, agility drills, and free running,
- (ii) single-leg plyometrics, cutting/pivoting drills with stutter step pattern, high intensity aerobic/anaerobic sport specific training, and advanced lower extremity strengthening,

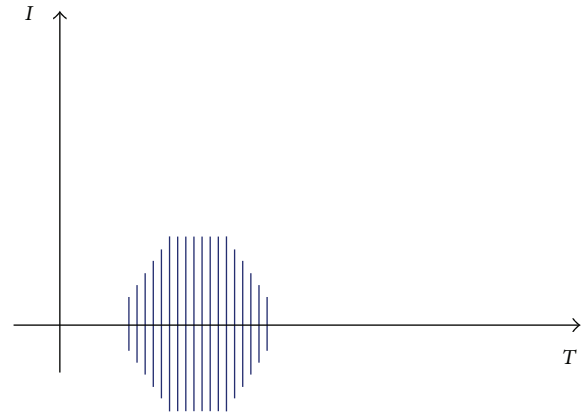


FIGURE 1: NMES impulse shape and characteristics. Legends: Base frequency: 2500 Hz, burst frequency: 50 Hz, on: 10 ms, off: 10 ms, increasing/decreasing ramp shape.

- (iii) triple hop for distance, single hop for distance, lateral hop 12'' × 12'' squares separated by 12'' of hops (in box), and unilateral vertical jump.

Weight training exercise in the gym was prohibited.

The individuals in group A additionally received neuromuscular electrical stimulation procedures on both right and left quadriceps (two electrodes on the muscle attachment sites). A portable electrical stimulator (Ionoson, Physiomed, Germany) delivered biphasic symmetric rectangular pulses (frequency of impulses 2500 Hz, train of pulses frequency 50 Hz). The stimulus output is interrupted every 10 ms to create “bursts” of stimulation every second. The 10 ms off period was not detectable by the subject. A total of 10 maximal contractions sustained for 10 seconds each with a 50 second off time defined a treatment session (according to methodology of stimulation prepared by Yakov Kots in year 1989 [10]—called in literature “Russian stimulation” and recognized as one of the types of the NMES—Figure 1). The intensity was between 55 and 67 mA (mean of 58.89 mA). Stimulation was performed with a current which produced strong, visible motion effects. Electrodes were made of conductive carbon rubber (8 × 6 cm). Before application of electrodes the skin was cleaned by use of alcohol. The total time of single procedure was 30 minutes. Quadriceps was stimulated at 60° of knee flexion. The procedures were repeated three times daily (3 hours of break between treatments), 3 days a week (Tuesdays, Thursdays, and Saturdays), for one month.

2.3. Measures. Measurements of muscle strength were performed by a tensometer (Accuro Sumer, Poland). The tensometer was composed of resistance lever, roller, and electronic momentum meter (Figure 2). The spectrum of measurement was between 0 and 500 Newton meters (Nm). The magnitudes of force moment were converted into Newtons (N). The tested legs were at 60° of knee flexion (we observed maximal strength of muscle when individuals were prepared to the measurements).

Change of muscle circumference was measured by a “tailor tape” 10 cm above the patella on the quadriceps. The



FIGURE 2: Tensometry.

measurements were performed before and after experiment (the measurements were in a supine position before the first and after the last NMES procedure).

The goniometry pendulum test was composed of a peripheral device and a personal computer with software. The peripheral device consisted of a goniometry compass and an interface system-transducer cooperated with the computer. The goniometry compass was composed of two thin metal arms (Figures 3(a) and 3(b)). One of the arms (immobile) was fixed in a special outlet that allowed changing the angle and length. The mobile arm was connected to the athlete's leg. The motion of the compass was measured by a miniptoelectronic transducer. The position of the transducer was measured (with a resolution of 12 bytes (B) on one revolution) and coded in a range from 0° to 360° (exact to 0.088°). The signal was transmitted to the interface. The software allowed readings of 100 positions of the compass per second.

Using the pendulum test, the spectrum (range) and ease of motion in knee (whether the movement was smooth, physiological, and free in examined axis) were measured and determined by the following parameters:

n : number of oscillations,

t : whole time of oscillations,

T : period of oscillations ($T = t/n$),

λ : logarithm decrement of suppression ($\lambda = \ln X_2/X_4$, where X_2 is a second amplitude during oscillations and X_4 is a fourth amplitude during oscillations,

β : suppression index ($\beta = \lambda/T$).

The number of oscillations (n) and whole time of oscillations (t) described the ease of knee motion. The period of oscillations (T) and suppression parameters (λ and β) assessed the spectrum of knee motion (Figure 4). The goniometry pendulum test was performed for analysis of NMES safety (to assess whether an increase in muscle mass and strength will change in the mechanics of the knee joint).

2.4. Follow-Up. The goniometry pendulum test was repeated 1 and 3 months after the study (79 athletes were measured in followup and only one participant from group B was excluded because of femoral neck fracture). The following procedure

was performed for analysis of electrical stimulation safety in long term results.

2.5. Statistical Analysis. The chi-squared independence test (greatest reliability level) and parametric t -test were used for analysis of indicators, which characterized individuals in both comparative groups. The normal distribution was checked by Shapiro-Wilk (for the null hypothesis that a sample came from a normally distributed population) and the chi-squared test (when the null hypothesis was true, also consider that a chi-squared test is a test in which this is asymptotically true, meaning that the sampling distribution-if the null hypothesis is true can be made to approximate a chi-squared distribution as closely as desired by making the sample size large enough). Recalling that the null hypothesis is that the population is normally distributed, if the P -value is less than the chosen alpha level, then the null hypothesis is rejected (i.e., one concludes that the data are not from a normally distributed population).

If the P -value is greater than the chosen alpha level, then one does not reject the null hypothesis that the data came from a normally distributed population (according to statistical estimation the population over 30–35 is needed for further analysis of normal distribution, so we had to include about 80 participants in two groups in this study and use the parametric tests). Analyzed distributions appeared normal and we received the Gauss decay in all comparisons.

The parameters before and after study were compared in groups by parametric t -test (for dependent variables). Differences in parameters between groups were evaluated with t -test (for the independent variables); for comparisons of experimental and follow-up results we used analysis of variance ANOVA to analyze the differences between group means and their associated procedures (such as "variation" among and between groups). In ANOVA setting, the observed variance in a particular variable is partitioned into components attributable to different sources of variation.

Two-sided P values of less than 0.05 were considered to be statistically significant.

3. Results

The groups studied were homogeneous in terms of all participant characteristics (Table 1) and initial muscle power and knee biomechanical parameters. After experiment the strength of quadriceps on the operated side in group A (NMES) increased from 645.9 to 893.4 N (28.7%, $P = 0.001$) and in group B (control) it increased from 648.6 to only 669.8 N (4.6%, $P = 0.04$). The comparison after 1-month therapy of relative changes of the muscle strength between both groups showed a significant difference in favor of stimulation (28.7% versus 4.6%, $P = 0.002$, and 95% confidence interval). The strength of quadriceps on nonoperated side in group A increased from 840.1 to 1089.8 N (30.1%, $P = 0.003$) and in group B increased from 840.4 to only 885.2 N (4.6%, $P = 0.04$). The comparison after 1-month therapy of relative changes of the muscle strength between both groups showed



FIGURE 3: (a) and (b) are Goniometry pendulum test.

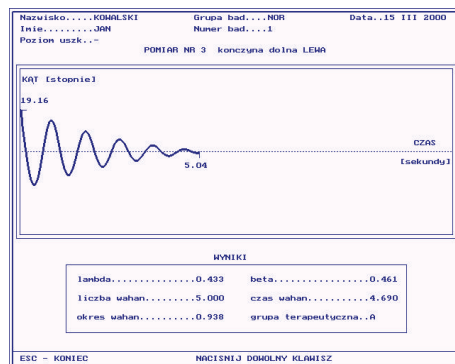


FIGURE 4: Exampled data from pendulum test (sinusoidal wave of pendulum movement). Legends: (lambda) λ : logarithm decrement of suppression. (beta) β : suppression index. (Okres wahan) T : period of oscillations. (Liczba wahan) n : number of oscillations. (Czas wahan) t : whole time of oscillations.

a significant difference in favor of stimulation (30.1% versus 4.6%, $P = 0.002$, and 95% confidence interval).

In NMES group on the operated side quadriceps circumference increased from 56.5 to 57.9 cm (1.4%, $P = 0.03$) and in group B it increased from 56.2 to 57.1 cm (0.6%, $P = 0.05$). The comparison after a month of treatment of relative changes of the muscle circumference between both groups showed a significant difference in favor of stimulation (1.4% versus 0.6%, $P = 0.04$, and 95% confidence interval). On the non-operated side quadriceps circumference increased from 58.1 to 59.3 cm (1.1%, $P = 0.03$) and in group B increased from 57.7 to 58.2 cm (0.4%, $P = 0.04$). The comparison after a month treatment of relative changes of the muscle circumference between both groups showed a significant difference in favor of NMES (1.1% versus 0.4%, $P = 0.04$, and 95% confidence interval).

The comparison of all parameters measured using goniometry pendulum test in group A and B did not indicate any significant difference and also in the followup (after 1 and 3 months after the end of study)—Tables 2 and 3.

4. Discussion

The results of this study showed that NMES is effective for muscle training in sport (we observed intensive increase of power and mass of quadriceps muscle after one month therapy), which corresponds with some research studies. However, experiments in the literature are usually based on small number of participants, unclear randomization (researchers do not use validated methods of randomization such as a computer or marked envelopes, only physician decides the allocation of participants), lack of inclusion and exclusion criteria, and no assessment of the safety of NMES application in sport [11, 13, 14, 19].

Paillard et al. [11] in their study observed the effects of different types of NMES programs on vertical jump performance. Twenty-seven healthy trained male students in sports-sciences were recruited and randomized into three groups. The control group (C group, $n = 8$) did not perform NMES training. Two other groups underwent 3 training sessions a week for over 5 weeks on the quadriceps femoris muscle—F group ($n = 9$): stimulation with an 80 Hz current for 15 min for improving muscle strength; E group ($n = 10$): stimulation with a 25 Hz current for 60 min for improving muscle endurance. The height of the vertical jump was measured before NMES training (test 1) and one week (test 2) and five weeks (test 3) after the end of the programs. The results showed that the height of the vertical jump significantly increased in both the F and E groups between tests 1 and 2 (5 cm and 3 cm, resp.). Results of test 3 showed that both groups preserved their gains. In authors opinion a NMES training program improves muscle strength.

British researchers [19] observed prolonged NMES in sedentary adults. Fifteen healthy subjects (10 men, 5 women) with a sedentary lifestyle completed a 6-week training program during which they completed an average of 29 1-hour of NMES sessions. The form NMES used by the subjects was capable of eliciting a cardiovascular exercise response without loading the limbs or joints. It achieved this by means of inducing rapid, rhythmical contractions in the large leg muscles. A crossover study design was employed with subjects undergoing their habitual activity levels during the nontraining

TABLE 1: Characteristics of individuals from group A and B.

	Group A	Group B	Level of significance
Number of participants	40	40	** $P > 0.05$
Age (years)			
Range	17–29	17–29	
Mean	22.4	21.3	* $P > 0.05$
SD	5.78	5.67	
Operated knee			
Right	26	23	** $P > 0.05$
Left	14	17	
Height (cm)			
Range	171–193	170–186	
Mean	180.3	176.5	* $P > 0.05$
SD	7.54	8.11	
Weight (kg)			
Range	71–80	63–100	
Mean	73.8	70.9	* $P > 0.05$
SD	5.76	7.12	
BMI (kg/m ²)			
Range	19.2–25.8	20.3–28.9	
Mean	22.4	23.4	* $P > 0.05$
SD	4.22	3.03	
Muscle strength (N)			
Operated	578.4–701.3	567.5–689.9	
Range	645.9	648.6	
Mean	34.6	38.6	
SD			** $P > 0.05$
Nonoperated			
Range	821.4–879.8	831.5–889.7	
Mean	840.1	840.4	
SD	23.4	27.9	
Duration of career (how long soccer players practice their discipline) in years			
Range	3.4–10.5	3.3–8.5	
Mean	5.4	4.8	* $P > 0.05$
SD	2.46	1.89	

* the t -test, ** the χ^2 -test.

phase of the study. The training effect was evaluated by means of a treadmill test to determine peak aerobic capacity, peak oxygen consumption, Vo_2 , a 6-minutes walking distance test, and measurement of body mass index (BMI) and quadriceps muscle strength. At baseline, the mean values for peak Vo_2 , 6-min walking distance, quadriceps strength, and BMI were

2.46 l/min, 493.3 m, 360.8 N, and 26.9 kg/m², respectively. After training, subjects demonstrated statistically significant improvements in all variables except BMI. Peak Vo_2 increased by an average of 0.24 l/min ($P < 0.05$), walking distance increased by 36.6 m ($P < 0.005$), and quadriceps strength increased by 87.5 N ($P < 0.005$). These results suggest that NMES can be used in sedentary adults to improve muscle strength.

Snyder-Mackler et al. [13] included 85 patients to treat with highintensity NMES, high-level volitional exercise, low-intensity NMES, or combined high and lowintensity NMES. All treatment was performed isometrically with the knee in 65 degrees of flexion. All of the patients participated in an intensive program of closed-kinetic-chain exercise. After four weeks of treatment, the strength of the quadriceps femoris muscle and the kinematics of the knee during stance phase were measured. Quadriceps strength averaged 70% or more of the strength on the uninvolved side in the two groups that were treated with high-intensity NMES (either alone or combined with low-intensity NMES), 57% in the group that was treated with high-level volitional exercise, and 5% in the group that was treated with low-intensity NMES. The kinematics of the knee joint were directly and significantly ($P < 0.05$) correlated with the strength of the quadriceps.

Other researchers [14] presented 27 healthy subjects (mean age 23.4 years) volunteered for the study and were randomly assigned to 1 of 3 groups; control group (no NMES); group 2 (NMES 2 times per week); and group 3 (NMES 3 times per week). Groups 2 and 3 received NMES (10 minutes per session) over a 4-week period for a total of 8 and 12 NMES training sessions, respectively. The isometric quadriceps femoris muscle force produced during NMES was monitored during each treatment minute. The force of the quadriceps femoris was assessed prior to the first week and at the start of weeks 2, 3, and 4 of the 4-week training program, with a final measurement after the fourth week (5 total measurements) for all subjects. Only the mean percent change in quadriceps power before and after the 4 weeks of training with NMES between the control group and group 3 was significantly different ($P = 0.021$).

In our research we studied motion and function parameters in knee, without analysis of inflammatory reaction or quadriceps muscle damage.

A review of the literature can be found to have only one article about muscle pathologies after NMES application. Vanderthommen et al. [17] studied the effects on muscle function of an electrical stimulation bout applied unilaterally on thigh muscles in healthy male volunteers. One group (ES group, $n = 10$) received consecutively 100 isometric contractions of quadriceps and 100 isometric contractions of hamstrings (on-off ratio: 6-6 s) induced by neuromuscular electrical stimulations (NMES). Changes in muscle torque, muscle soreness (VAS), muscle stiffness, and serum creatine kinase (CK) activity were assessed before the NMES exercise (preex.) as well as 24 h, 48 h and 120 h after the bout. A second group (control group, $n = 10$) was submitted to the same test battery as the stimulation group and with the same time-frame. The between group comparison indicated a significant increase in VAS scores and in serum levels of CK

TABLE 2: Goniometry pendulum test in group A.

Parameter	Followup								Level of significance
	Before therapy		After therapy		1 month		3 months		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
λ									
Operated	0.57	0.19	0.56	0.16	0.55	0.20	0.55	0.22	$P > 0.05$
Nonoperated	0.47	0.18	0.45	0.19	0.46	0.22	0.46	0.22	*(in all comparisons)
β [s ⁻¹]									
Operated	0.77	0.30	0.77	0.28	0.74	0.22	0.75	0.30	$P > 0.05$
Non-operated	0.57	0.30	0.56	0.31	0.53	0.23	0.54	0.30	*(in all comparisons)
T [s]									
Operated	0.89	0.30	0.94	0.30	0.95	0.27	0.93	0.30	$P > 0.05$
Non-operated	0.95	0.22	0.99	0.19	0.99	0.19	0.98	0.21	*(in all comparisons)
n									
Operated	3.32	1.22	3.32	1.43	3.31	1.21	3.32	1.25	$P > 0.05$
Non-operated	4.78	1.22	4.87	1.45	4.86	1.21	4.87	1.21	*(in all comparisons)
t [s]									
Operated	2.07	1.22	2.07	1.52	2.12	1.10	2.13	1.21	$P > 0.05$
Non-operated	3.04	1.20	3.04	1.45	3.01	1.13	3.01	1.13	*(in all comparisons)

* Analysis of variance ANOVA.

Legends:

λ : logarithm decrement of suppression (more than 0.65 is pathology of I Outbridge degree of the articular cartilage), β : suppression index (more than 0.85 is pathology of I Outbridge degree of the articular cartilage), T : period of oscillations (less than 0.75 is pathology of I Outbridge degree of the articular cartilage), n : number of oscillations (less than 3.00 is pathology of I Outbridge degree of the articular cartilage), and t : whole time of oscillations (less than 1.50 is pathology of I Outbridge degree of the articular cartilage).

TABLE 3: Goniometry pendulum test in group B.

Parameter	Followup								Level of significance
	Before therapy		After therapy		1 month		3 months		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
λ									
Operated	0.55	0.21	0.58	0.19	0.56	0.22	0.55	0.20	$P > 0.05$
Nonoperated	0.48	0.21	0.43	0.19	0.44	0.22	0.45	0.20	*(in all comparisons)
β [s ⁻¹]									
Operated	0.75	0.32	0.76	0.21	0.75	0.22	0.75	0.28	$P > 0.05$
Non-operated	0.58	0.27	0.57	0.28	0.55	0.25	0.54	0.28	*(in all comparisons)
T [s]									
Operated	0.87	0.34	0.90	0.35	0.90	0.29	0.90	0.30	$P > 0.05$
Non-operated	0.95	0.19	0.97	0.19	0.97	0.19	0.99	0.20	*(in all comparisons)
n									
Operated	3.35	1.31	3.33	1.38	3.33	1.30	3.33	1.30	$P > 0.05$
Non-operated	4.75	1.31	4.79	1.39	4.80	1.41	4.80	1.41	*(in all comparisons)
t [s]									
Operated	2.11	1.03	2.09	1.04	2.10	1.11	2.11	1.01	$P > 0.05$
Non-operated	3.10	1.28	3.11	1.25	3.11	1.11	3.10	1.09	*(in all comparisons)

* Analysis of variance ANOVA.

Legends:

λ : logarithm decrement of suppression (more than 0.65 is pathology of I Outbridge degree of the articular cartilage), β : suppression index (more than 0.85 is pathology of I Outbridge degree of the articular cartilage), T : period of oscillations (less than 0.75 is pathology of I Outbridge degree of the articular cartilage), n : number of oscillations (less than 3.00 is pathology of I Outbridge degree of the articular cartilage), and t : whole time of oscillations (less than 1.50 is pathology of I Outbridge degree of the articular cartilage).

only in the ES group. In the ES group, changes were more pronounced in hamstrings than in quadriceps and peaked at 48 h (quadriceps VAS scores = 2.20 ± 1 (0 at preex.); hamstrings VAS scores = 3.15 ± 2.14 (0 at preex.); hip flexion angle = $62 \pm 5^\circ$ ($75 \pm 6^\circ$ at preex.); CK activity = $3021 \pm 2693 \text{ IU} \cdot \text{L}^{-1}$ ($136 \pm 50 \text{ IU} \cdot \text{L}^{-1}$ at preex.). The results of the study suggested the occurrence of muscle damage that could have been induced by the physiologically incorrect muscle recruitment in NMES and the resulting overrated mechanical stress.

In our study the NMES appeared to be safe for biomechanics of knee joint. Based on our previous experience we can strongly recommend the goniometry pendulum test as useful diagnostic method in physical therapy process [20]. The purpose of this clinical study was to assess low frequency, low intensity magnetic fields in the enhancement of the physical rehabilitation of patients after knee endoprosthesis surgery. The study included 62 patients who underwent total knee arthroplasty. Group A consisted of 32 patients who were physically rehabilitated. Group B consisted of 30 patients who were physically rehabilitated and treated additionally with pulsing magnetic fields (5 mT, 30 Hz, 20 min once a day, 5 days weekly). Therapy lasted for 3 weeks for both groups. The rehabilitation process was evaluated using a goniometer, tensometer, goniometry pendulum test, Lysholm scale for knee function, and a visual analogue scale (VAS) questionnaire for pain and activity. The pendulum test appeared very useful for precise observation of biomechanical changes in knee joint during therapy process. The physical therapy decreased the logarithm decrement of suppression (λ) by about 7.9% in group A and 9.6% in group B, suppression index (β) decreased; about 11% in group A and 13.3% in group B. The period of oscillations increased by 4.9% in group A and 4% in group B; number of oscillations (n) increased by 22.1% in group A and 20.6% in group B. The whole time of oscillations increased of 29.8% in group A and 24.5% in group B.

In our study we did not observe both early and long term results (goniometry pendulum test our research is the first attempt in literature of using this apparatus in sport) any pathological changes in knee function after increasing the strength and mass of quadriceps in use of NMES. The progress in muscle parameters did not have influence pathologically on knee function.

4.1. Limitations of Study. In our study soccer players after a month of therapy with NMES + rehabilitation or only rehabilitation program (7 months after ACL reconstruction) returned to sport and league competition, what could interfere with follow-up observation. We were not able to demonstrate a relationship between the pendulum test and muscle dysfunction either in the study or from previous research using a similar protocol correlated with markers of muscle damage. We tried to use objective measurement methods, but we did not collect data related to functional outcomes, of which there are some they could have chosen (triple-hop, crossover-hop, and jump-landing test).

5. Conclusion

The results of this study show that NMES (presented parameters in experiment) is useful for strengthening the quadriceps muscle in soccer athletes. There is an evidence the benefit of the NMES in restoring quadriceps muscle mass and strength of soccer players. In our study the neuromuscular electrical stimulation appeared to be safe for biomechanics of knee joint. The pathological changes in knee function were not observed.

Conflict of Interests

The authors would like to certify that they have no commercial associations with the manufacturers of the equipment described in the paper or other conflict of interests.

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