

Nutrition and Dementia

Guest Editors: Fabio Coppedè, Paolo Bosco, Andrea Fuso, and Aron M. Troen





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Current Gerontology and Geriatrics Research

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Editorial

Nutrition and Dementia

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Dementia is a progressive decline in the ability to remember, learn, understand, and communicate. Alzheimer's disease (AD) represents the most common form of dementia in the elderly, affecting about 28 million individuals worldwide. Current treatments for AD and other dementias are sorely limited, falling short of preventing or significantly slowing disease progression. Worldwide, the number of people afflicted by AD is expected to exceed 100 million by 2050, as a result of the increased life-span expectancy in both developed and developing countries [1]. Compelling epidemiological observations suggest that human nutrition and lifestyle factors can modify the risk of late onset dementia. For example, overweight in midlife has been associated with an increased risk for dementia in late life [2], and frequent consumption of fruits and vegetables, fish, and omega-3 rich oils is associated with decreased AD risk. Dietary patterns such as the "Mediterranean diet," characterized by high intake of vegetables, legumes, fruits, cereals, and unsaturated fatty acids have also been associated with decreased risk of developing mild cognitive impairment (MCI) and of MCI conversion to AD [3]. There is also evidence that higher intake and status of specific nutrients such as vitamin E, vitamin B12, and folate may be protective against cognitive decline and aging [4]. Similarly, intake of antioxidants, such as vitamin E and C, and fatty fish have been found to be protective against vascular dementia (VaD) risk, whilst fried fish intake and elevated homocysteine are associated with increased risk [5].

Despite this, evidence for the cognitive benefit of nutritional and lifestyle interventions in age-associated cognitive impairment and dementia remains equivocal, and a clear

elucidation of mechanisms remains elusive. Although some good evidence is available for the beneficial effect of nutritional interventions on neurocognitive outcomes [6], most large scale nutritional randomized clinical trials to date have failed to clearly demonstrate efficacy in mitigating cognitive impairment and dementia (as well as other chronic conditions). This gap between the epidemiological evidence and interventional trials has prompted a critical re-evaluation of conceptual and practical limitations of clinical trials of nutritional interventions and the need for better trial design [7–9], while at the same time redoubling efforts in fundamental research to clarify the underlying pathophysiological mechanisms of the indicated interventions.

This special issue presents timely review articles and research papers covering several aspects of nutrition in dementia providing a forum for the critical evaluation and delineation of new approaches and opportunities for nutritional and lifestyle interventions. Three papers in this issue address the role of obesity in dementia. R. Businaro et al. reviewed the molecular mechanisms linking obesity to AD risk, focusing on the correlation between the onset and progression of the disease and the stress-induced changes in lifestyle, leading to overnutrition and reduced physical activity, ending with metabolic syndrome and obesity. Particularly, the authors reviewed the factors leading to alterations of energy metabolism in favour of visceral fat accumulation and the subsequent promotion of insulin resistance and chronic inflammation, both critical factors for AD initiation and progression. They also discussed strategies to reduce abdominal fat deposits and their beneficial role on cognitive decline in a comprehensive and updated review article. It

is clear from this review that hyperinsulinemia is one of the most frequent endocrine features in overweight people leading to insulin desensitization and represents a risk factor for cognitive decline. This point was discussed also by L. Moll and M. Schubert that reviewed the literature dealing with the role of insulin and insulin-like growth factor-1 in the pathogenesis of obesity-associated dementia, with focus on the possible contribution of forkhead-box transcription factors (FoxO). FoxO are mediators of insulin and insulin-like growth factor-1 involved in several processes including neuronal proliferation, differentiation, stress response, and β -amyloid detoxification. In this original review article, the authors discuss the few studies performed so far in animal models to investigate the possible contribution of FoxO-mediated transcription to AD pathology. Studies in *C. elegans* are in conflict with those performed in mice that suggest that FoxO-mediated transcription does not protect against but rather increase amyloid pathology. However, the small number of published papers limits our understanding of the role of this pathway in dementia, and additional research is required to fully address this interesting topic. It is also noteworthy that FoxO-mediated transcription is not the only mediator of the insulin and insulin-like growth factor-1 cascade, and that several factors might therefore be involved in the pathogenesis of dementia. As an example, insulin resistance and inflammation, observed in people with an excess of visceral adiposity, are also believed to contribute to metabolic deterioration of skeletal muscle, manifesting clinically as sarcopenia. M. E. Levine and E. M. Crimmins investigated the influence of insulin resistance and inflammation on the association between body composition and cognitive performance in older adults. The study included 1127 adults from the US National Health and Nutrition Examination Survey (NHANES 1999–2002) and showed that body composition does not predict cognitive functioning in adults aged 60–69 years, but, for adults aged 70 years and over, sarcopenia and obesity, either independently or concurrently, were associated with worse cognitive functioning (WAIS III, Digit Symbol substitution performance) relative to nonsarcopenic nonobese older adults. Cognitive functioning was lowest among the sarcopenic obese group, and sarcopenic obese people also showed the highest levels of inflammation. Moreover, insulin resistance accounted for a significant proportion of the relationship between cognitive performance and obesity, with or without sarcopenia. This is a novel, interesting, and important study on the association between sarcopenic obesity, insulin resistance, and cognitive functioning strengthened by the large sample size and suggesting that individuals who are sarcopenic obese have a lower cognitive ability than other subjects, and that this association might be partially explained by insulin resistance and inflammation. Aging seems also to be an important factor to be considered in order to see a significant effect. The study has, however, several limitations that the authors have acknowledged, including the lack of longitudinal data to evaluate whether insulin resistance precedes frailty and cognitive decline, the use of a single measure of cognitive functioning to study cognitive performance, and the fact that insulin resistance and inflammation were measured only one

point in time. However, it provides preliminary interesting data for the design of longitudinal studies to better address this issue. Collectively, these three papers provide new insight into the role that obesity, metabolic syndrome and sarcopenia might play in dementia, by focusing on possible biological mechanisms or by providing novel and interesting preliminary data on humans.

G. L. Bowman et al. analysed 36 subjects with mild-to-moderate AD investigating the correlation between dyslipidemia and blood-brain barrier (BBB) impairment. The CSF-to-serum ratio of albumin (CSF Albumin Index) ≥ 9 was considered as BBB impairment. The study revealed that dyslipidemia was frequent in AD subjects with BBB impairment. Furthermore, patients with BBB dysfunction showed significantly higher mean plasma triglyceride and lower HDL cholesterol levels with respect to those without BBB dysfunction. Overall, plasma triglycerides explained 22% of the variance in BBB integrity and remained significant after correcting for age, gender, *APOE- $\epsilon 4$* genotype, blood pressure, and statin use. This research paper adds to the growing literature on BBB dysfunction in AD by suggesting that dyslipidemia may have a detrimental role in maintaining BBB integrity in mild-to-moderate AD. The limit of this study is the very small sample size, and additional studies are required to demonstrate a causal link between dyslipidemia and BBB impairment. However, if replicated in other populations, these findings might gain clinical significance because dyslipidemia is treatable.

Another important issue is that of the difficulties associated with maintaining adequate nutrition in individuals with dementia. Nutrition and appetite decline with age, often accompanied by weight loss. This is particularly critical in advanced dementia where progressive feeding problems can become so severe that physicians and families must decide whether artificial nutrition and hydration is required. This important issue is discussed in the review article by G. A. Pivi and colleagues.

B vitamins and methyl-group homeostasis have received considerable attention in recent years, providing a basis for understanding the complex interplay between nutrition and epigenetic modifications of disease-related genes, including those that are involved in aging and in Alzheimer's disease. For example, experimental modification of methyl-group homeostasis through dietary deficiency and supplementation of choline and folate has been shown to exert profound effects on brain development, function, and aging [10–12], including epigenetic modification and/or aberrant expression of key AD genes [13]. In light of this attention, it has been turned to the potential impact of food folic acid fortification and nutritional status in human metabolic programming [14, 15].

Nicotinamide methylation is another potentially important mechanism that is theoretically susceptible to altered methylation potential, but one that is far less studied. Dietary impairment of this pathway might contribute to disturbed energy metabolism and cholinergic neurotransmission in dementia. A. C. Williams and colleagues draw attention to the role that this pathway may play in age-related cognitive impairment, by taking pellagra, as an example, a severe

vitamin deficiency disease most commonly caused by a chronic lack of niacin (vitamin B3) in the diet, and leading to dementia, dermatitis, diarrhoea, and death. Niacin status is not well studied in relation to dementia risk, either alone or in relation to methyl-group metabolism although there are experimental animal data showing benefits of supplementation [16]. More research in this area is warranted.

Overall, it is becoming clear that dietary factors play a fundamental role in brain health throughout the lifespan. Improving nutrition and dietary habits during early life and adulthood might therefore be an effective strategy to counteract age-related diseases.

We hope that this special issue will contribute to our understanding of the complex interplay between nutrition and dementia and thereby advance our collective efforts to prevent, delay, and manage this debilitating disease.

We are extremely grateful to all the authors for their contributions that made possible to cover several timely topics in this special issue.

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Review Article

Alzheimer's Disease Promotion by Obesity: Induced Mechanisms—Molecular Links and Perspectives

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The incidence of AD is increasing in parallel with the increase in life expectancy. At the same time the prevalence of metabolic syndrome and obesity is reaching epidemic proportions in western populations. Stress is one of the major inducers of visceral fat and obesity development, underlying accelerated aging processes. Adipose tissue is at present considered as an active endocrine organ, producing important mediators involved in metabolism regulation as well as in inflammatory mechanisms. Insulin and leptin resistance has been related to the dysregulation of energy balance and to the induction of a chronic inflammatory status which have been recognized as important cofactors in cognitive impairment and AD initiation and progression. The aim of this paper is to disclose the correlation between the onset and progression of AD and the stress-induced changes in lifestyle, leading to overnutrition and reduced physical activity, ending with metabolic syndrome and obesity. The involved molecular mechanisms will be briefly discussed, and advisable guide lines for the prevention of AD through lifestyle modifications will be proposed.

1. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60–80% of cases, although there is growing awareness that AD is often confused with other causes of dementia. According to estimates by 2006, approximately 33.9 million people worldwide have AD [1], and Alzheimer's Association estimates 5 to 3 million people in the US have the disease [2]. It is foreseen that the prevalence will nearly triple [1] or increase from three to four times, according to other studies, in the next 40 years due to demographic changes and a longer life expectancy [3]. Among the sixty year olds, those who show a higher prevalence are North Americans (6.4%) and Western Europeans (5.4%). For the rest there is 4.9% in Latin America. It is to outline that incidence is likely to increase in proportion to the aging population, which by 2030 would increase by 250% in industrialized countries. Previous data show that rates of dementia increase exponentially with age [4]. The incidence

of dementia doubles every 5 years, from 0.66/100 persons aged 70 to 74 years to 11.30/100 persons for those aged 90 or more.

A bulk of studies has provided evidence to support the role of obesity as a risk factor for AD development and the possible role of psychosocial factors (e.g., professional achievements, stimulant mental activities, social engagement, and physical activity) as protective factors.

1.1. Stress in Modern Societies That Influences AD. "Lifestyle has dramatically changed in modern societies and social psychological stress is ubiquitous and universally pervasive. In modern life, statistics show powerful effects of early-life stress, concurrent chronic stress, and socioeconomic status with sociopolitical system have a potent effect on the burden of chronic disease" [5].

Increasing evidence has been accumulating about the role of stress as an important challenge to the onset and progression of AD [6]. The heterogeneous nature of AD is

only partly explained by the brain's propensity to accumulate aberrantly processed, misfolded, and aggregated oligomeric structural proteins, including amyloid- β peptides and hyperphosphorylated tau.

2. Globesity

Obesity and the metabolic syndrome are challenging public health issues since their prevalence in Western populations has reached epidemic proportions. In 1997 the World Health Organization (WHO) stated that "...obesity should now be regarded as one of the greatest neglected public health problems of our time..." During the last four decades the world has experienced an epidemic of overweight individuals and the WHO has predicted a "globesity epidemic" with more than 1 billion adults being overweight and at least 300 million of these being clinically obese [7]. In the United States approximately 65% of adults are overweight or obese [8], and almost half of Italian men and about 1 of 3 Italian women are overweight or obese [9].

The excess of adiposity is an established risk factor for the development of cardiovascular diseases, type 2 diabetes, and hypertension, all characterized by resistance to insulin-mediated glucose disposal. Insulin resistance and the compensatory hyperinsulinemia associated with insulin resistance have been shown to be independent predictors of all three clinical syndrome [10]. Several studies have reported that obesity, generally defined as a body mass index BMI > 30, increases the risk of disease and all-cause mortality and reduces life expectancy [11]. Caucasian individuals, who reached a BMI > 40 between the ages of 20–29 years, could expect a reduction in remaining years of life expected by approximately 6 and 12 years, respectively [11, 12]. Obesity has not only been linked to reduced life expectancy but also to accelerated aging, as demonstrated by obese women having telomeres that were 240 bp shorter compared to lean women of similar age [13].

Many factors influence the onset of obesity, including genetic, environmental, socioeconomic, behavioral, and/or psychological factors. The main cause that leads to the development of obesity is a positive energy balance, which consists in imbalance between energy intake and expenditure, lasting for several years. Such a balance is regulated by a complex network of signals that connect the endocrine system with the central nervous system [14]. Overnutrition, leading to obesity, impairs systemic metabolic homeostasis and is a metabolic stressor associated with intracellular organelles (e.g., the endoplasmic reticulum) stress. Starvation and malnutrition can impair immune function too [15].

Different kinds of stressors, including life stressful events, on the other hand, have been particularly linked to development of visceral obesity [16]. The hypothalamic-pituitary-adrenal axis and the central and peripheral components of the autonomic nervous system constitute the two main vital stress-system functions [5]. States of over- or under-nutrition may impair the crosstalk between metabolic and immune system, leading to the activation of the immune response and the development of a "low-grade systemic

inflammation," as confirmed by increasing circulating levels of proinflammatory cytokines, adipokines and other inflammatory markers detected in obese subjects. Activation of the immune response in obesity is mediated by specific signaling pathways, with Jun N-terminal kinase and I κ appaB kinase beta/nuclear factor kappa-light-chain-enhancer of activated B cells being the most studied. It is known that the above events modify insulin signaling and result in the development of insulin resistance [16].

2.1. Visceral Fat (VF) and Subcutaneous Fat (SF). Increased body mass induces the formation of fat deposits in the visceral and subcutaneous structures [12]. Fat tissue is at present considered as an active endocrine organ with a high metabolic activity. It produces several mediators that are important in metabolism (adipokines) and inflammation (cytokines). Many of these cytokines also referred to as "adipokines," including leptin, TNF- α , IL-6, heparin-binding epidermal growth factor (HB-EGF), and vascular endothelial growth factor (VEGF) among others, may play an important role in many diseases by promoting angiogenesis, inflammation, cell proliferation and insulin resistance [12].

Activation of proinflammatory pathways and secretion of cytokines such as interleukin-6 (IL-6), plasminogen-activator inhibitor-1, and free fatty acids (FFA) have been suggested to produce insulin resistance [17, 18]. Fat accumulation in the abdominal area is considered one of the main risk factors for developing cardiovascular and metabolic diseases. This effect is probably depending on cytokines synthesized by visceral adipose tissue and released into the portal circulation, thereby reaching the liver, where they can trigger a series of inflammatory events, including greater FFA and glycerol release [19]. In particular the proinflammatory cytokine IL-6 regulates hepatic protein synthesis by evoking an acute phase response such as C-reactive protein (CRP) or serum amyloid-A. As reported by Libby and colleagues, the Quebec Heart Study has shown that obesity is associated with systemic inflammation, since there is a correlation between VF and the levels of CRP [20]. Studies in rodents and humans have revealed that body fat distribution, including VF, SF, and ectopic fat is critical for determining the risk posed by obesity [21].

VF secretes more cytokines than subcutaneous adipose tissue; in addition using either waist circumference and/or waist-to-hip ratio as a proxy of abdominal obesity, numerous studies have found that VF is a stronger risk factor for metabolic and cardiovascular diseases than body mass index (BMI) or other fat depots. Adipose tissue can produce several modulators of inflammation. This condition promotes the development of diabetes mellitus (DM) which is accompanied by an increased risk of both macrovascular and microvascular disease. The negative impact of obesity on cognitive function may be, at least in part, due to vascular defects, impaired insulin metabolism and signaling pathway or a defect in glucose transport mechanisms in brain. It is plausible to hypothesize that increased vascular dysfunction at the level of the brain may in turn affect memory function [22].

In a study performed on male C57BL/6 mice fed a standard diet low in fat until the age of 6 weeks and then switched to a high fat diet for the following 15 or 21 weeks, it has been shown that obese mice exhibited a higher concentration of macrophages in visceral adipose tissue compared to lean animals [23].

VF is associated with a low-grade inflammation due to the increased secretion of numerous pro-inflammatory cytokines from adipocytes and their associated macrophages [12]. In this connection, our previous results showed that in obese children, the presence of a chronic low-grade inflammation corresponds to a shift to Th1-cytokine profile dominated by the production of IFN-gamma, accompanied by insulin resistance [24]. However, the molecular basis for the association between obesity and low-degree chronic inflammation is still unknown.

2.2. AD Can Be Considered a Metabolic Disease. Diabetes mellitus (DM) is a risk factor for nongenetic AD. Recent studies in humans indicate that insulin signaling is impaired in the AD brain [25]. Insulin is the hormone in charge of tis-sutal glucose uptake, it binds to specific receptors expressed on cell membranes and triggers the phosphorylation of cellular substrates. A switch from a tyrosine phosphorylation to a serine phosphorylation of the insulin receptor substrate (IRS) family of proteins impairs the metabolic activity of insulin leading to insulin resistance and type 2 diabetes. This alteration may be mediated by stress and inflammation, as shown by the effects of cytokines released by immune cells. Insulin receptors and insulin-sensitive glucose transporters have been detected at the level of the medial temporal region of the brain that supports memory formation, leading to hypothesize that insulin may be involved in maintaining normal cognitive function [22]. Moreover, AD is associated with cerebrovascular amyloid angiopathy in which an increased expression of RAGE (receptor for advanced glycation endproducts) was detected. Carbohydrate-derived advanced glycation endproducts (AGEs) have been implicated in the chronic complications of DM and have been reported to play an important role in the pathogenesis of AD [26]. They have been localized in AD brain and their presence was shown to be significantly increased in human post-mortem samples of AD with diabetes compared to AD without diabetes or nondemented controls [27]. RAGE has been found to be a specific cell surface receptor for amyloid β , thus potentially facilitating neuronal damage [28, 29].

A recent paper by de la Monte [30] discusses the direct relationship between impaired insulin/IGF signaling, increased amyloid- β precursor protein (A β PP) synthesis, and the increased accumulation of A β peptide in amyloid plaques, promoting neurodegeneration. The mechanism proposed by de la Monte is that brain insulin deficiency and resistance cause neuronal death due to trophic factor withdrawal, deficits in energy metabolism, and inhibition of insulin-responsive gene expression, including those required for acetylcholine homeostasis. It is known that insulin resistance increases with age and that normal blood glucose levels are maintained until the body is able to provide an adequate

amount of insulin (hyperinsulinemia). As described above, peripheral insulin resistance is mediated by the inflammatory process that takes place within adipose tissue, enlarging abdominal fat in obese individuals. As a matter of fact, insulin resistance is a common finding in chronic inflammatory diseases and, in particular, it is believed that increased adipose-derived inflammatory cytokines induce a chronic inflammatory state that not only increases cardiovascular risk, but also antagonizes insulin signaling and mitochondrial function thereby impairing glucose homeostasis [31, 32].

2.3. Energy Metabolism Dysregulation. The decreased energy metabolism due to insulin resistance first and then to reduced glucose uptake impairs ATP production. Chronic inflammation, such as detected in obesity and stress conditions, implies a constant, although low-grade, activation of the immune system, as evidenced by the increased serum levels of proinflammatory cytokines in subjects suffering from chronic inflammatory diseases. In this connection, Straub et al. [33] reported that neuroendocrine pathways are involved in energy regulation: inflammation induces an increase in cortisol serum levels, by stimulating HPA axis and sympathetic nervous system (SNS), ending with sickness behavior, characterized by strong reduction of muscle, brain, and gut activity. Fat gain depends, inter alia, on a lack of physical activity which brings to muscle loss and increased leptin levels which, in turn, support muscle loss and fat gain, leading to cachectic obesity [33]. In this respect it is to remind that proinflammatory cytokines can disturb insulin receptor and IGF-1 receptor signaling [34] and that FFA induce insulin resistance [35].

As a result, insulin resistance produces a dysregulation of energy balance at the level of liver, adipose tissue, and muscle and, at the same time, favours the activated cells of the immune system since they do not become insulin resistant. Leptin, whose release is increased following the enlargement of fat, stimulates glucose uptake by immune cells and therefore their metabolic activity. In this way a vicious circle takes place, with a continuous release of proinflammatory adipokines such as TNF, IL-6, resistin and leptin which contribute to maintain a chronic inflammatory state. Several inflammatory pathways have been shown to contribute to metabolic dysregulation at several levels, among them the modulation of insulin signalling is perhaps the most crucial, as it is a highly conserved and dominant metabolic pathway in nutrient and energy homeostasis. In addition to cytokines, many of the inflammatory signalling pathways that inhibit insulin receptor signalling are directly triggered by nutrients, such as circulating lipids. Other inflammatory pathways are induced by organelle stress owing to nutrient overload and processing defects and result in metabolic stress. These complexes connections are schematically depicted in Figure 1.

2.4. Obesity and Systemic Inflammation. Macrophage accumulation and the subsequent local inflammation are believed

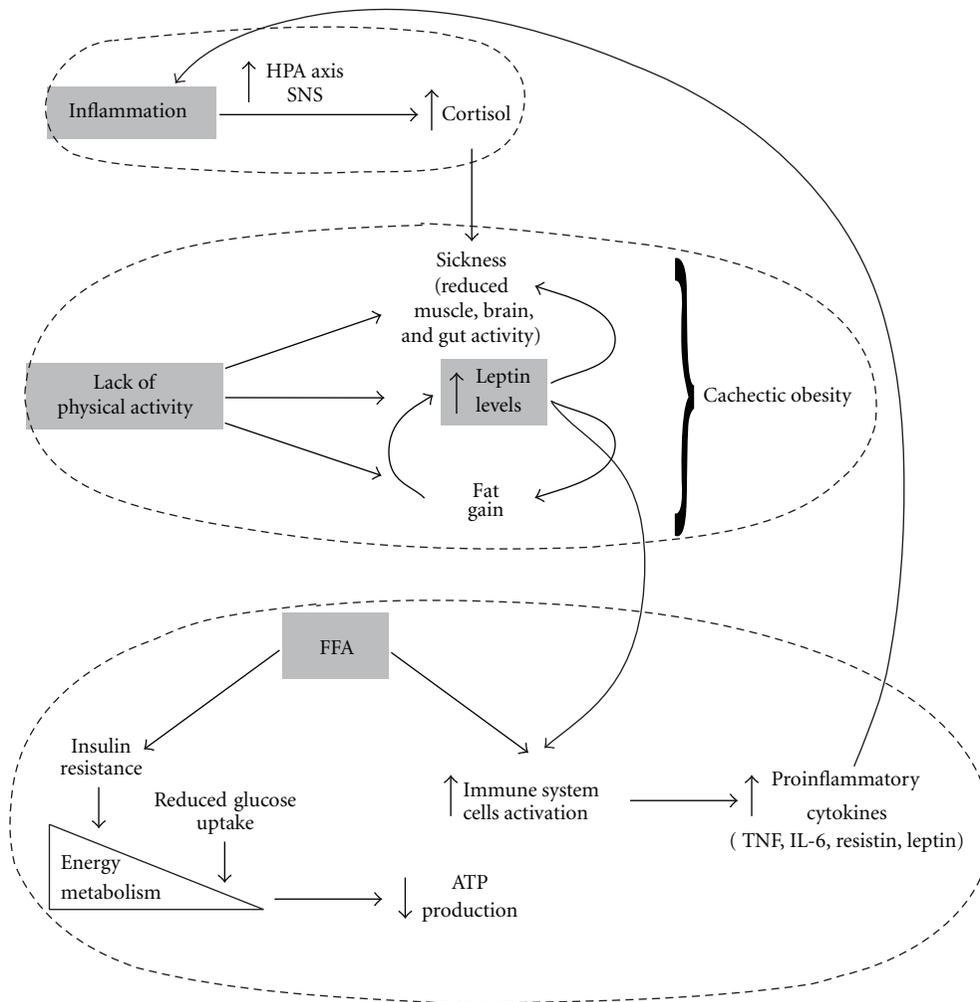


FIGURE 1: The complex and interconnected pathways linking stress, inflammation, obesity and energy metabolism.

to result in numerous metabolic dysfunctions that accompany obesity, including systemic inflammation. Macrophages and adipocytes are closely related and share many functions: for example, they both secrete cytokines and can be activated by pathogen-associated components, such as lipopolysaccharide (LPS) [36]. Preadipocytes have been shown to transdifferentiate into macrophages, and transcriptional profiling has suggested that macrophages and pre-adipocytes are genetically related [37].

AD was recently added to the obesity-related diseases taking into account the release of inflammatory cytokines by activated macrophages in visceral adipose tissue. Several recent studies prospectively assessed the predictive value of elevated pro-inflammatory cytokines for the risk of developing AD in cognitively intact individuals or for aggravating AD symptoms in patients who were already diagnosed with the disease. Higher plasma levels of the inflammatory marker α 1-antichymotrypsin and IL-6 [38], as well as higher spontaneous production of IL- 1β or TNF- α by peripheral blood mononuclear cells [39], were found to be associated with increased future risk of AD in older individuals.

The Framingham Heart Study comprising male participants (age range 55–88 years) followed up over a period of 18 years revealed that obesity had an adverse effect on cognitive performance [40]. In agreement with this finding, Osher and Stern described that obesity may contribute to the reduction of cognitive skills observed in AD [41].

In the otherwise healthy older population, the combination of expansive waist circumference or BMI, with high systolic or diastolic blood pressure, was linked to a modest decrease in performance on tests of motor speed, manual dexterity, and executive function [42]. The association appeared to be so profound that the risk for AD increased by 36% for every BMI unit at the age of 70 years.

Crosstalk between lymphocytes and adipocytes can lead to immune regulation. Adipose tissue produces and releases a variety of proinflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines, such as TNF- α , IL-6, monocyte chemoattractant protein 1 (MCP-1), and others. Proinflammatory molecules produced by adipose tissue have been implicated as active participants in the

development of insulin resistance and increased risk of cardiovascular disease associated with obesity [43].

2.5. Cytokines, Adipose Tissue and AD. Immune system influences central nervous system through the release of cytokines targeting different brain districts. Cytokines mediate not only immune response but also neuron functions and survival [44]. They may originate from peripheral immune cells and reach the CNS by crossing the blood-brain barrier or may be directly produced within the CNS by neurons and glial cells [45]. Cytokines bind to specific cytokine receptors on neurons and glial cells thereby directly influencing brain function. Two main clusters of cytokines have been recognized, based on the specific T-helper cells producing them: type 1 helper cells, generally engaged in cellular immune response and type 2 helper cells involved in humoral immunity.

Cytokines are commonly classified in two categories: interleukin-1 (IL-1), tumor necrosis factor α (TNF- α), interferon γ (IFN γ), IL-12, IL-18 and granulocyte-macrophage colony stimulating factor (GM-CSF) are well characterized as pro-inflammatory cytokines whereas IL-4, IL-10, IL-13 and transforming growth factor- β (TGF- β) are recognized as anti-inflammatory cytokines.

2.6. Adipokines. The family of adipokines is continuously expanding and includes also INF γ , LIF (Leukemia Inhibiting Factor) and chemokines such as the MCP-1 and MIP-1 (Macrophagic Inflammatory Protein-1). TNF- α is secreted by the activated macrophages and by adipocytes and plays an important role in the defence of the host from infections and in the development of the Th-1 subpopulations; it is involved in the pathogenesis of autoimmune diseases such as the multiple sclerosis, rheumatoid arthritis, and I type diabetes. Patients affected by insulin resistance present increased TNF- α levels and mice with a TNF- α deficiency are protected by the insulin resistance-induced obesity.

Leptin is a typical adipokine produced in proportion to the amount of the body fat; indeed its levels are related to BMI. It has been shown that there is a direct link between leptin, leptin receptor, and activation of mTOR (mammalian target of rapamycin) [46]. Leptin and nutrients (i.e., amino acids and glucose) show pulsatile secretion in vivo and living cells continuously adjust their gene expression in response to the changing milieu that influences the energy status into the cells and modulates cell growth, proliferation, and differentiation. The maker of this mechanism is the mammalian target of rapamycin (mTOR), an evolutionarily conserved 289-kDa serine-threonine protein kinase that is inhibited by rapamycin [47]. Within this context, it has been hypothesized that leptin might act as an endogenous "sensing" factor that could act as a critical link among environment (availability of nutrients), metabolism, and immune responses [48]. Pro-inflammatory activity of leptin, that potentiates T helper 1 (Th1) immune responses, is due to decreased Treg cell proliferation [49, 50]. Matarese and colleagues showed that the leptin/mTOR signalling pathway influences Treg cell responsiveness according to

the energy metabolism. High metabolic rate determines Treg cell hyporesponsiveness sustained by mTOR activation, whereas inhibition of mTOR with rapamycin enhances Treg cell proliferation and their anti-inflammatory activity [47]. Leptin-mTOR overexpression in freshly isolated Treg cells is responsible for their state of hyporesponsiveness. The hypothesis that a metabolic control of immune-mediated pathogenesis of obesity and obesity-related insulin resistance exist [51, 52], has recently reinforced the concept that metabolism and proliferation of lymphocytes can impact, at different levels, the control of inflammation, autoimmunity, and immune-mediated disorders [48, 53]. In all of these conditions, Treg cells have a high metabolic state, high ATP and mTOR activity and are unresponsive to regulatory action in immune/inflammatory response [54]. Blood leptin levels are directly correlated with adiposity [55, 56]. In the presence of excessive food intake, aggravated by psychological stress, the increase of leptin induces activation of mTOR that determines adverse effects on age-related diseases and inhibition of autophagy in the liver (lipophagy) which contributes to steatosis and lipid accumulation in VF [57]. In the hypothalamus, leptin inhibits food intake through mTOR activation, and mTOR inhibition with rapamycin prevents leptin-induced anorexia [58, 59].

In a condition of lack of food and consequent reduction of the body fat mass, low levels of leptin lead to a reduced metabolic waste to preserve the energy necessary to support the functions of vital organs such as heart, kidney, and brain; on the other hand, the finding of high levels of leptin in obese subjects has been interpreted as the result of relative leptin resistance at the level of nervous central system. As explained before, although the effects of leptin can favour survival in adverse conditions such as fast, it induces immune alterations blocking the precursor of Treg in favour of the Th17 clone. Adipocyte-derived IL-17 plays a crucial role in the development of chronic inflammation, autoimmunity, insulin resistance [60] and, in our opinion, in the promotion of AD. Leptin interferes with insulin signalling and in type 2 diabetes plasma leptin levels were found to be correlated with the degree of insulin resistance; therefore, insulin resistance syndrome is accompanied by hyperleptinemia as well as hyperinsulinemia [61, 62]. In obese patients leptin and TNF- α induce endothelial dysfunction and oxidative stress [63]. Only in body mass of lean individuals leptin regulates insulin action in the peripheral circulation, decreases brain beta-secretase levels and modulates A β turnover [64]. Severe obesity is depending on a lack of leptin signalling due to mutation of leptin itself (ob/ob) or the leptin receptor (db/db) resulting in an increase of food intake concomitant with a reduction of energy expenditure. The main mechanisms of leptin resistance previously described are (i) leptin failure to cross the blood-brain barrier because a downregulation of leptin transporter (as LepRa or LepRe), (ii) hypothalamic LepRb downregulation, (iii) abnormalities in the leptin receptor signalling pathways, as inhibition of the JAK2-STAT3 pathway, overexpression of SOCS-3, impairment of PI3K-mTOR pathway or more recently of the ERK pathway [59].

So therefore, hyperleptinemia is a sign of leptin-resistance and this leptin resistant state was associated with impaired activation of the PI3K/AKT pathway and a hyperstimulation of mTOR pathway [65].

As mentioned before, VF secretes more cytokines than subcutaneous adipose tissue and as obesity takes place, several proinflammatory factors in adipose tissue are produced. Moreover, adipocytes size is an important determinant of leptin synthesis, since larger adipocytes contain more leptin than smaller ones [66]. Therefore, summarizing we can say that local inflammation triggered by macrophage accumulation results in numerous metabolic dysfunctions that accompany obesity and bring to the development of systemic inflammation [67]. As evidenced by the work of De Rosa et al. [50] high levels of leptin put Treg cells in an anergic state, leading to the activation of Th1 cells and the release of several inflammatory mediators with a development of that chronic inflammatory state repeatedly reported in obese patients.

As outlined before, though the portal circulation the cytokines reach the liver, where they can stimulate hepatic inflammation thereby inducing a chronic systemic inflammatory response and release of toxic FFA. FFA have long been known to produce deleterious effects on pancreatic beta-cell function inhibiting insulin production and inducing insulin resistance [68] whereas in parallel proinflammatory cytokines, such as TNF- α , alter insulin receptors [69].

2.7. Adipokines and AD: Protective Role of Leptin. Recent reports have shown that in addition to its action on the hypothalamus, leptin may also exert its effect on the cortex and on the limbic areas, which are involved in cognitive and emotional regulation of feeding behavior [70].

Leptin roles on brain structure and function are being extensively characterised by studies showing that human brain is highly neuroplastic and depends on leptin for its proper development. Additional studies in different populations need to confirm the role of leptin as a biomarker for neurodegenerative diseases.

Some evidence links adipokines directly to cognition. The adipoinsular axis—with leptin and insulin as its main components—has central roles on the regulation of brain function [71]. Leptin regulates food intake and energy metabolism binding to specific regions of the hypothalamus. Recently it has been shown that leptin has extra-hypothalamic effects that may protect the brain against the development of mood and neurodegenerative disorders, such as AD [70, 72]. Leptin appears to exert important effects on brain development as leptin-deficient rodents display abnormal brain development and leptin actively participates in the development of the hypothalamus [73] and in the processes of learning and memory, especially during aging: it was actually described a specific effect in the CA1 region of the hippocampus, selectively altered in AD [74]. Leptin is a potent neurogenic factor not only to hippocampal but also to cortical neurons [75] and has neuroprotective actions against glutamatergic cytotoxicity and oxidative stress [76]. In addition, leptin was shown to promote the proliferation of

neuronal precursors as observed following intracerebroventricular administration of a lentiviral vector encoding leptin. After 3 months of treatment the number of proliferating hippocampal cells was increased, as judged by morphometric analysis and by the attenuation of A β -induced neurodegeneration [77]. By decreasing the accumulation of intraneuronal lipids, leptin suppresses amyloidogenic pathways. In addition, by inhibiting GSK-3b (the most relevant tau kinase), leptin reduces protein tau phosphorylation, inhibiting the formation of neurofibrillary tangles. The inhibitory effects of leptin on the formation of senile plaques and neurofibrillary tangles seem to be mediated by the selective activation of AMPK in neurons. Leptin was previously shown to reduce the amount of extracellular A β , both in cell culture and animal models and its chronic administration resulted in a significant improvement in the cognitive performance of transgenic animal models [78]. In AD, weight loss often precedes the onset of dementia and the level of circulating leptin is inversely proportional to the severity of cognitive decline. It is speculated that a deficiency in leptin levels or function may contribute to systemic and CNS abnormalities leading to disease progression. Furthermore, leptin deficiency may aggravate insulin-controlled pathways, known to be aberrant in AD [78]. As a matter of fact, significantly lower plasma levels of leptin in AD patients compared to the controls were detected [79].

More recently, low leptin levels have been implicated as a direct cause of cognitive impairment, particularly AD [79]. In that case, the absence of beneficial effects of leptin in the central nervous system would predispose to cognitive impairment. However, the protective effect of leptin against the development of AD was observed only among lean individuals; on the contrary obese humans, despite having high leptin levels, may not benefit from protective effects of leptin because of central leptin resistance. In this way a paradoxical situation takes place: leptin is a neuroprotective factor, counteracting AD cognitive impairment, as confirmed by the clinical observation that a weight loss precedes AD manifestations and is accompanied by reduced serum levels of leptin. On the other hand, obese patients exhibit high levels of leptin that cannot perform their protective effects since leptin resistance has been induced at the level of CNS. Other studies are needed to elucidate the molecular mechanisms promoting leptin resistance.

2.8. Insulin Resistance in AD. Brain glucose metabolism was found to be impaired in AD [80] and the Rotterdam study and others that followed [81, 82] established that type 2 diabetes mellitus increases the risk for developing cognitive impairment and dementia in AD. In that case, insulin resistance and low insulin levels in the CNS (interestingly referred as “*diabetes of the brain*”) would lead to the accumulation of A β and cognitive impairment. Cerebrovascular and central inflammation would contribute further to the pathogenesis of AD [72, 83]. As reported by Hölscher in 2011 [84], a common observation for type 2 diabetes and AD is the desensitization of insulin receptors in the brain. Insulin acts as a growth factor in the brain and shows neuroprotective

properties, activating dendritic sprouting, regeneration, and stem cell proliferation. The impairment of growth factor signalling such as early insulin receptor desensitization has been suggested to be involved in the cascade of neurodegenerative events leading to AD [80, 84]. Recently animal models that reflect the pathologic conditions of both type 2 diabetes and AD, were generated. APP23 transgenic mice, a well-established animal model for AD were crossed with ob/ob mice or polygenic NSY mice, as a model for diabetes. Taking advantage of this experimental model, it has been demonstrated that a diabetic condition enhances cognitive dysfunction with cerebrovascular changes such as vascular inflammation and cerebral amyloid angiopathy and that neuropathological changes are associated with impairment of brain insulin signaling [83].

In addition, low insulin levels and insulin resistance can contribute to a decrease in acetylcholine levels, which represents a possible biochemical link between diabetes mellitus and AD [85, 86].

Human and experimental animal studies revealed that neurodegeneration associated with peripheral insulin resistance is likely mediated via a liver-brain axis whereby toxic lipids, including ceramides, cross the blood brain barrier and cause brain insulin resistance, oxidative stress, neuroinflammation, and cell death [87]. Recent evidence demonstrates that sphingolipid metabolism is dysregulated in obesity and specific sphingolipids may provide a common pathway that link excess nutrients and inflammation to increased metabolic and cardiovascular risk [88]. Insulin resistance promotes lipolysis, and lipolysis generates toxic lipids, that is, ceramides, which further impair insulin signalling, mitochondrial function, and cell viability [89]. Cytotoxic ceramides cause insulin resistance by activating proinflammatory cytokines and inhibiting insulin-stimulated signalling through PI3 kinase-Akt [90].

2.9. Stress and Leptin. As described above, we may argue that obesity itself is a known risk factor for AD, especially in the presence of psychological stress. It is well known that people with depression, especially older adults, have reduced cognitive performance. In addition, many people with dementia also have depression. This illness is associated with elevated levels of cortisol and cytokines which may directly damage the hippocampus and increase the risk of dementia and depression [6, 91]. Depression is frequently a prodrome of dementia and the incidence of depression among patients with AD is estimated to be greater than 40% [92].

Social stressors have effects on food intake and adiposity and, in this case, the individuals with psychological stress have elevated plasma insulin and leptin concentrations compared to nonstressed humans [93]. Glucocorticoids (GC) and insulin interact in the upregulation of serum leptin concentrations. In presence of psychological chronic stress GC lead to overeating and to obesity in spite of elevated leptin concentrations [94]. When the stressor is viewed as a threat without resources to change the coping well with, the stress response is the HPA axis activation and it is a potent trigger

of cortisol release [95]. Social stressors have various effects on food intake and adiposity: for example subordinate rats show elevated plasma insulin and leptin concentration compared to dominant animals [96]. Increased GC concentrations have been associated with VF accumulation and with insulin resistance as well as leptin resistance [97]. In humans, the co-elevation of insulin and cortisol is depending from comfort food preference (high fat and sweet food). Palatable comfort food promotes dependence activating brain reward system comprising opioids, dopamine and endocannabinoid. Leptin resistance produces impaired “brake” that in part explain the epidemic “globesity” of eating without metabolic need [98]. The relationship between stress and food intake in humans may also involve effects of GC on NPY, CRH, leptin as well as opioids. It is worthwhile to note that GC receptor density is increased in VF compared to SF and stimulates lipolysis in the whole body [99, 100].

Cortisol increase in presence of insulin inhibits lipid mobilization and promotes the differentiation and proliferation of adipocyte. Increased GC concentration has been associated with insulin and leptin resistance. Those adiposity signals play a role not only in energy regulation but also on the brain reward system by continued search for additional comfort food [101]. Stress-induced cortisol exposure may impair right prefrontal cortex activity, thus impeding the more reflective cognitive control over eating [102]. Therefore, leptin stimulation caused by GC promotes “leptin resistant” obesity and, in turn, obesity may contribute to the reduction of cognitive skills observed in AD. Results from other published studies demonstrate an association of obesity with deficits in learning, memory, and executive functioning in human patients [103, 104]. This relationship between obesity and cognitive impairment has also been documented in experimental animals [105–107]. Collectively, results from the study of Pistell and colleagues reinforce the link between diet-induced obesity and cognitive loss and suggest potentially causal roles for high levels of dietary fats and increased brain inflammation in driving obesity-induced cognitive disruption [108].

Prolonged exposure to proinflammatory cytokines impairs synaptic plasticity, contributing to cognitive and mood disorders [109]. TNF- α and IL-1 β , whose receptors are specifically present at the level of hypothalamus, hippocampus and cortex, were shown to impair neuronal plasticity.

Notably, recent collective reports indicate that after brain injury and in neurodegenerative disorders neurogenesis is controlled by cytokines, chemokines, neurotransmitters, and reactive oxygen/nitrogen species (ROS), which are released by dying neurons as well as by activated macrophages, microglia, and astrocytes [110].

2.10. Age-Related Conditions That Can Be Largely Prevented or Delayed by Lifestyle Interventions

2.10.1. Nutritional and Dietary Factors. The studies reported above strongly suggest that alterations of energy metabolism in favor of VF accumulation promote insulin resistance and

a chronic inflammatory status which have been recognized as important cofactors in AD initiation and progression. From this, it follows that a preventive strategy should include a reduction of abdominal fat deposits, through a proper nutrition tailored to the individual needs. [12]. Great importance in this respect are showing the modern technologies for analysis of body composition that determine fat mass, fat free mass, total body water, intra- and extracellular water, mineral, metabolism and inflammatory status in the body (BIA-ACC and TomEEEx devices) [111, 112]. In fact, thanks to these noninvasive and low cost technologies, it is possible to acquire information on the above parameters and follow up the changes induced in the low level inflammatory status secondary to modifications in lifestyle, especially in diet and physical activity [113–115].

Several follow-up studies have already reported that decreased AD risk is associated with increasing dietary or supplementary intake of antioxidants (e.g., vitamins E and C, fruits and vegetables). A diet high in antioxidants may reduce inflammation, which is associated with the risk of dementia [92]. A variety of dietary supplements have been reported to be beneficial for learning in animals and humans [116]. Positive effects on brain function have been reported for fish oil, teas, fruits, folate, spices, and vitamins [117]. Particularly interesting are plant-derived products such as grapes, blueberries, strawberries, tea, and cocoa, which benefit memory in rodents [118]. Furthermore, studies found that higher adherence to “Mediterranean diet” (i.e., a dietary pattern with higher intake of fish, fruits, and vegetables rich in antioxidants) produced beneficial effects in AD patients. On the contrary diets enriched with saturated fats and cholesterol increase the risk, which is reversed by polyunsaturated fatty acids and fish. Fatty acids may also play a part in the synthesis and fluidity of nerve cell membranes, in synaptic plasticity and neuronal degeneration. In addition, oxidative stress is one of the central features in the AD brain. Thus, it may be plausible that supplementation or diet rich in antioxidants such as fruits, vegetables, and vitamins E and C might protect against AD.

B vitamins were particularly investigated in clinical studies with the attempt to define an association between serum levels of these vitamins and the risk of dementia and AD and different intervention trials were made obtaining, unfortunately, discordant results. As a matter of fact, the Cochrane systematic review concluded that folic acid and vitamin B12 supplementations have no benefits on cognition, although folate plus vitamin B12 are effective in reducing plasma homocysteine.

Folate (vitamin B9), vitamin B12, and vitamin B6 are cofactors in the reactions responsible for homocysteine (Hcy) transformation and removal in the “so called” one-carbon metabolism [119]. Plasma levels of these three vitamins are therefore strictly related to Hcy levels; according to a general paradigm, high plasma Hcy (hyperhomocysteinemia, HHcy) is related to low B vitamin levels. After many studies in humans and in animal models, it is now accepted that moderate HHcy is a potential risk factor for AD, although the possibility that it represents just a marker of the process exists, the association of low B vitamins with

AD is still more controversial [120]. However, the majority of retrospective studies evidenced increased Hcy levels in AD subjects and prospective studies pointed out that HHcy is evident before AD development, stressing the idea of a causative function of HHcy in AD [121].

On the basis of these considerations, few interventional studies were performed to evaluate the potentially beneficial supplementation with B vitamins in the attempt to lower Hcy levels and improve cognitive functions. Only one of these studies demonstrated that Hcy-lowering intervention was associated to the improvement of the effects of cholinesterase inhibitors therapy; other studies demonstrated that B vitamin supplementation was able to reduce Hcy levels but did not improve cognitive status or delay cognitive decline [122]. The apparent controversial results obtained after observational and interventional studies in AD patients are probably due to undisclosed biases and methodological troubles occurring in the design of these protocols. Firstly, the most evident (as well as incomprehensible) aspect of the interventional studies on B vitamin supplementation conducted so far is that subjects recruited for the trials had normal Hcy levels; in some case, HHcy was among exclusion criteria. We should suppose that individuals with normal Hcy levels do not present any alteration in one-carbon metabolism; therefore, B vitamin supplementation can very unlikely result in evident beneficial effects. The second aspect to be taken into account is the duration of the trial, since quite short treatments were done in some of these studies. Moreover, the high variability in the doses used for the B vitamin supplementation makes difficult to compare the results obtained from different trials. Finally, appropriate (sensitive) cognitive tests able to reveal subtle differences and larger (more variable) populations could improve the results of the interventional trials with B vitamins supplementation in AD.

2.10.2. Physical Activity. The risk for dementia and AD was also increased in older people with increasing social isolation and less frequent and unsatisfactory contacts with relatives and friends. In fact several studies indicate that a poor social network or social disengagement is associated with cognitive decline and dementia. Rich and large social networks also provide affective and intellectual stimulation that could influence cognitive function and different health outcomes through behavioral, psychological, and physiological pathways [123].

It has also been shown that low-intensity activity such as walking may reduce the risk of dementia and cognitive decline and experimental studies in animal models have established a direct correlation between physical exercise and neurogenesis, especially in the hippocampus [124]. Physical activity is important also in promoting brain plasticity, and it may also affect several gene transcripts and neurotrophic factors that are relevant for the maintenance of cognitive functions. A strong protective effect of regular physical activity in middle age against the development of dementia and AD in late life was reported, especially for persons with the APOE4 allele.

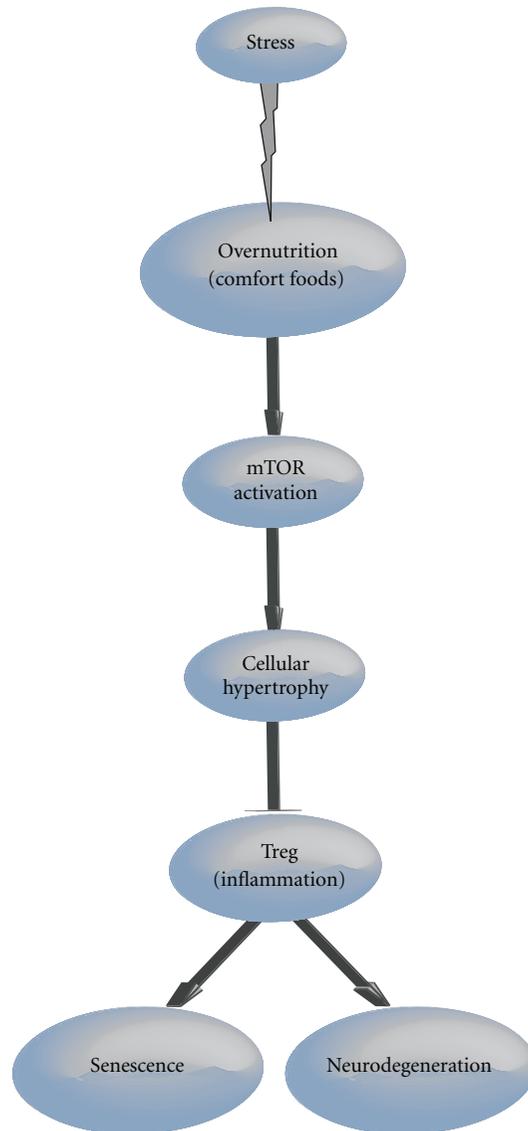


FIGURE 2

So regular exercise and intellectual stimulation may represent those useful mild stresses that should stimulate maintenance and repair pathways and cause adaptation of cells and the ability to tolerate stronger stresses [125].

An important role in influencing the life span has been attributed to the tissue pH which is related to the metabolites of various nutrients. In a recent study dealing with the yeast chronological life span model it has been shown that acidification of the medium accelerates yeast aging [126]. A central player of this effect has been identified by TOR pathway: when the cell cycle is blocked but mTOR is still active, it causes hypertrophic, hyperactive, hyperfunctional phenotype, with compensatory resistance to signals such as insulin and growth factors, switching quiescence into senescence; therefore, TOR limits life span by accelerating age-related diseases [125]. By contrast, the deletion of either TOR1 or SCH9/S6K seems to extend yeast chronological

life span in part by depleting ethanol and acetic acid [127]. These updates support the important role of tissue pH, which should not be acidified by foods high in protein (meat, cheese). “Anti-inflammatory” foods, such as diets rich in fruits and vegetables, may prevent osteopenia and cachectic obesity with an important buffer action and possibly at negative PRAL (potential renal acid load).

3. Conclusion

The schematic diagram (Figure 2) illustrates our suggested link between stress, obesity, and Alzheimer’s Disease. At the center of the system a series of events, that begin and are maintained by psychosocial stress, trigger the inflammation due to immunological dysregulation that arises from dys-metabolic processes caused by high energy intake.

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Review Article

The Role of Insulin and Insulin-Like Growth Factor-1/FoxO-Mediated Transcription for the Pathogenesis of Obesity-Associated Dementia

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Epidemiological studies suggest that being obese in midlife is a risk factor for cognitive decline and dementia in later life. Hyperinsulinemia is one of the most frequent endocrine features in overweight people which results in insulin desensitization. Thus, chronically high insulin levels have been identified as risk factor for dementia. Accordingly, chronically high insulin levels might be harmful for brain function. Furthermore, insulin and IGF-1-induced signaling is reduced in the brains of patients suffering from Alzheimer's disease (AD). Interestingly, studies in rodents suggest that reduced insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1R) signaling decrease AD pathology, that is, β -amyloid toxicity. Data obtained in *C. elegans* indicate that the beneficial effect mediated via reduced IR/IGF-1R signaling might partially be induced via the forkhead-box O transcription factors (FoxO). In the mammalian brain, there are FoxO1, FoxO3a, and FoxO6 expressed. Surprisingly, high-fat diet specifically reduces the expression of FoxO3a and FoxO6 suggesting that IR/IGF-1 \rightarrow FoxO-mediated transcription is involved in the pathogenesis of obesity-associated cognitive impairment. Therefore, the function of FoxO1 and FoxO3a has been investigated in animal models of Alzheimer's disease in detail. The current paper focuses on the role of IR/IGF-1 signaling and IR/IGF-1 \rightarrow FoxO-mediated transcription for the pathogenesis of obesity-associated dementia.

1. Introduction

Obesity is characterized by a body mass index (BMI) of over 30 kg/m². The prevalence of obesity will rise to approximately 700 million people worldwide in 2015 [1]. Furthermore, midlife overweight and obesity might increase the risk for dementia during aging [2–4]. Hence, the role of obesity or overweight status in the development of cognitive decline or dementia is a major health concern and possibly associated with enormous health care costs. Prospective investigations on the role of BMI for the development of dementia did not provide a conclusive picture, yet. Some studies report no association or even decreased BMI to be associated with dementia or Alzheimer's disease [5, 6], and others

suggested higher BMI to be a risk factor for dementia [7] or that overweight in middle age is associated with dementia decades later [8, 9]. It seems to be difficult to estimate the exact role of obesity itself for the initiation or progress of cognitive impairment. Furthermore, obesity is associated with a variety of cardiovascular risk factors influencing long-term cognitive performance. Moreover, lower cognitive abilities are a risk factor for obesity, but on the other hand, dementia in later life might be associated with lower BMI. Thus, it might well be that obesity in younger or midlife is a risk factor for dementia, and dementia is causing weight loss and cachexia on the long run. Taken together, cognitive performance might influence the pathogenesis of obesity and being overweight the development of cognitive impairment,

dementia, and neurodegeneration. This interrelationship between body weight and cognitive function implicates the need for lifetime studies and standardized tests to identify cause or consequences of obesity-associated dementia. The complex interplay might at least partially explain the different results obtained by different studies. However, there is growing evidence that disturbed metabolic signals in obesity or type 2 diabetes feedback to the central nervous system (CNS) influencing brain function and possibly the pathogenesis of dementia or cognitive decline.

Recently, insulin and insulin-like growth factors (IGFs) have been suggested as important modifiers for the pathogenesis of neurodegenerative diseases, providing a link between obesity, type 2 diabetes (T2D), and cognitive impairment or even the pathogenesis of Alzheimer's disease. An important key mediator of insulin and IGF-1-mediated effects are the forkhead box O (FoxO) transcription factors. These transcription factors are involved in the neuronal proliferation, differentiation, stress response, and β amyloid detoxification.

The current review discusses the role of insulin and insulin-like growth factor-1/FoxO-mediated transcription for the pathogenesis of obesity-associated dementia from model organisms to humans.

2. Obesity and Dementia

As mentioned above, there might be a complex interplay between cognition and metabolic signals between the peripheral blood and the CNS. Obesity is associated with a whole variety of metabolic signals feeding back to the brain for example, leptin, insulin, or different cytokines. Furthermore, timing of "metabolic injuries" might be crucial for cognitive function during later life. Thus, it is not surprising that epidemiological studies show different results depending on the study collective, duration of study, phase of life investigated, and comorbidities (e.g., T2D).

In detail, Stewart and coworkers showed that in a prospective, population-based study of Japanese American men over a 32-year period that (dementia-associated) weight loss begins before the onset of the clinical syndrome and accelerates by the time of diagnosis [6]. Thus, weight loss is part of the clinical presentation of patients suffering from dementia, for example, AD. Another study showed a link between an increased BMI and the risk to develop Alzheimer's dementia in elderly people 10 years before the onset of symptoms, suggesting that the period in life of being overweight might be an important issue [7].

Interestingly, there are several studies supporting the hypothesis that obesity in midlife plays a role in the development of dementia in later life [8, 9].

The possible role of the surveillance periods of exposure to overweight for cognitive function during life has recently been reviewed by Elias and coworkers [10]. In addition, the Swedish Adoption/Twin Study of Aging (SATSA) focused on the relation of BMI and cognitive decline over a time period of over 40 years. This study showed an association of higher

BMI in midlife and cognitive decline in males and females [11]. Furthermore, the Finnish Twin Cohort Study revealed that the BMI in midlife as well as cardiovascular risk factors are associated with reduced cognitive abilities during aging [12].

Taken together, low BMI and weight loss seem to be the first clinical manifestation of neurodegeneration even before the onset of perceivable cognitive impairment. However, even still heterogeneous, recent data suggest that certain periods of exposure to obesity during life might be crucial for cognitive function during aging.

3. Hyperinsulinemia and Dementia

Chronic hyperglycemia impairs cerebral blood flow [13] as well as central glucose utilization [14]. Interestingly, central insulin ameliorates cognitive function, and acute central insulin administration leads to improved spatial memory in mice [14]. Accordingly, intranasal application leads to increased verbal memory in humans [15]. In the Nurses' Health Study (NHS), nondiabetic women with higher fasting insulin levels tended to have lower performance on global and verbal cognition. Furthermore, higher levels of fasting insulin were associated with faster rates of cognitive decline [16]. However, insulin levels were relatively low in this study indicating a potential role of even modestly elevated insulin concentrations. In the Physicians' Health Study, higher late-life fasting insulin levels among nondiabetic men were associated with a greater subsequent decline in general cognition [17]. Taken together, insulin in the short run might improve cognition, but chronically elevated insulin levels are associated with faster cognitive decline during aging. Thus, alterations of insulin levels and insulin-mediated signals/transcription might be an interesting candidate to explain the association of obesity and dementia.

4. Insulin/Insulin-Like Growth Factor-1 Signaling

Insulin receptors (IRs) are present in the so-called classic insulin responsive tissues such as muscle, fat, or liver and nonclassic tissues such as brain, endothelial cells, or gonadal cells. In 1978, Havrankova et al. demonstrated for the first time the localization of IRs in the CNS, an organ classically considered as an insulin-insensitive tissue. Moreover, insulin enters the CNS across the blood brain barrier through an active transport mechanism [18–21]. The localization of insulin receptors in the CNS was assessed by various techniques, including *in vitro* binding studies [22], *in vivo* and *in vitro* autoradiography and computerized densitometry [21–25] and immunocytochemistry [26]. According to these studies, insulin receptors are widely distributed in the brain with highest concentrations in the olfactory bulb, hypothalamus, cerebral cortex, and hippocampus.

The insulin and IGF-1 receptor (IR/IGF-1R) are tyrosine kinases which consist of a membrane bound domain with

tyrosine kinase activity. This tyrosine kinase phosphorylates tyrosine residues of downstream signaling proteins like insulin receptor substrates (IRSs). The IR and IGF-1R have a heterotetrameric structure with extracellular localized α -subunits and membrane bound β -subunits. These β -subunits contain ATP-binding motifs, autophosphorylation sites, and tyrosine protein kinase activity activated after binding of insulin or IGF-1 to the receptor [27–29]. Binding of the ligand results in conformational change of the receptor and induces autophosphorylation followed by recruitment of IRS proteins which get thereby tyrosine phosphorylated. The IRS protein family consists of four members, IRS-1 to 4 [30–32]. These IRS proteins consist of an pleckstrin homology (PH) domain located at the N-terminus, a phosphotyrosine-binding (PTB) domain and a C-terminus with multiple tyrosine phosphorylation sites. These phosphotyrosine motifs of the IRS proteins are binding sites for Src homology (SH)2 domain-containing proteins [33]. Furthermore, the PH domain interacts with phosphoinositides, while the PTB domain binds to phosphotyrosine residues of, for example, the IR and IGF-1R [34–36]. Insulin induces tyrosine and serine phosphorylation of IRS-1 which leads to positive or negative regulation of IRS-1 and the downstream signaling pathway [37–39]. The mammalian phosphatidylinositol (PI) 3-kinase family consists of classes I to III, and class I is subdivided into classes Ia and Ib [40]. PI3K, a class Ia kinase, induces phosphorylation of the 3' hydroxyl position of phosphatidyl-myoinositol lipids [41]. The PI3K shows a heterodimeric structure with a catalytic 110 kDa subunit which is noncovalently bound to a 50-, 55-, or 85 kDa regulatory subunit. After binding and activation of IRS to the IR or IGF-1R, the PI3K is recruited to the membrane using the p85 regulatory subunit. Additionally, the growth factor receptor binding protein (GRB)-2 and the SH2-phosphatase (SHP) 2 are recruited after activation of the IR/IGF-1R signaling pathway. Activation of the PI3K leads to phosphorylation of phosphatidylinositol diphosphate (PI_{4,5}P) to generate phosphatidylinositol triphosphate (PI_{3,4,5}P). The phosphorylation of PI_{4,5}P is reduced via PTEN (phosphatase and tensin homolog deleted on chromosome ten) action. Following this step, the downstream signaling proteins like phosphoinositide-dependent protein kinase (PDK) and protein kinase B (PKB, AKT) are activated. PDK has two isoforms, PDK-1 and PDK-2. PDK-1 phosphorylates AKT at Thr308 [42–44]. AKT is a serine/threonine kinase with a size of 57 kDa. AKT occurs in three isoforms, AKT-1 to AKT-3. The structure of AKT consists of a PH domain, a kinase domain, and an N- and C-terminal regulatory subunit [45]. In addition to the PI3K pathway, insulin and IGF-1 activate the MAP kinase (MAPK, mitogen-activated protein kinase) signaling cascade (Figure 1) [36, 46, 47].

5. Forkhead-Box O Transcription Factors

FoxOs differ in their expression pattern. FoxO1 and FoxO3a are ubiquitously expressed. In contrast, FoxO6 only occurs in the brain, whereas FoxO4 has not been found in the brain so far [48, 49]. FoxO1 is predominantly expressed in the dentate

gyrus, striatum, and ventral hippocampus, while FoxO3a mainly occurs in the cerebellum, cortex, and hippocampus. FoxO6 is found in the hippocampus, amygdala, and cingulate cortex of the adult murine brain [50, 51].

Activated AKT phosphorylates forkhead-box O transcription factors which leads to binding of 14-3-3 inducing their nuclear exclusion. This inactivates FoxO-mediated transcription which regulates apoptosis, growth, metabolism, and cellular differentiation under active conditions [52].

The mammalian FoxO transcription factor family contains 4 proteins: FoxO1, FoxO3a, FoxO4, and FoxO6. These proteins share a conserved DNA binding domain, the forkhead domain (FKHR) binding to a consensus FoxO-recognized element (FRE) sequence of the target gene (G/C)(T/A)AA(C/T)AA [48, 53, 54]. Target genes of FoxO-mediated transcription are, for example, Fas ligand (FasL), p27^{KIP1} [55, 56], and manganese superoxide dismutase (MnSOD) [57] (Figures 2 and 3).

FoxO-mediated transcription is regulated via posttranslational modifications. One major modification is the phosphorylation of different sites within FoxOs. Upon activation, AKT phosphorylates FoxO1 at Thr24, Ser256, and Ser319 [53, 59–62]. FoxO3a becomes phosphorylated at Thr32, Ser253, and Ser315 via AKT [63]. Furthermore, FoxOs are phosphorylated via different kinases depending on the stimulus (review in [64]). Other posttranslational modifications are ubiquitination. FoxO1 is ubiquitinated via Skp2, the substrate-binding component of the Skp1/culin 1/F-box protein (SCF^{Skp2}) E3 ligase complex. This ubiquitination occurs after phosphorylation of FoxO1 at Ser256 via AKT [65–68]. FoxO1 and FoxO3a are polyubiquitinated, while FoxO4 is monoubiquitinated for degradation [69]. Additionally, FoxO transcription factors are methylated, for example, FoxO1 gets methylated at Arg248 and Arg250. These sites are located in the AKT phosphorylation motif. This methylation is promoted by the protein arginine N-terminal methyltransferase 1 (PRMT1) protecting FoxO1 from phosphorylation via AKT, translocation out of the nucleus, and degradation [70]. Furthermore, FoxOs are acetylated via CBP and p300 with their interacting proteins like CBP- and p300-associated factor (PCAF) [71]. The acetylation of FoxOs decreases DNA binding and promotes phosphorylation of FoxO via AKT which inactivates FoxOs [72, 73]. Deacetylation of FoxOs is induced by silent information regulator 1 (SIRT1), a nicotinamide-adenine-dinucleotide- (NAD-) dependent histone deacetylase [74, 75].

FoxO-mediated transcription is involved in several processes. One of them is controlling cell cycle arrest via regulation of transcription of, for example, the cyclin-dependent kinase inhibitor p27 (review in [76]). Under conditions of growth factor deprivation, the IR/IGF-1R signaling pathway is inactive, and FoxOs are active inducing cell cycle arrest and quiescence to promote survival [57]. Additionally, FoxOs are involved in oxidative stress response (Figures 2 and 3). To counteract reactive oxygen species (ROS) produced during oxidative stress, FoxOs increase expression of antioxidant enzymes like MnSOD [57].

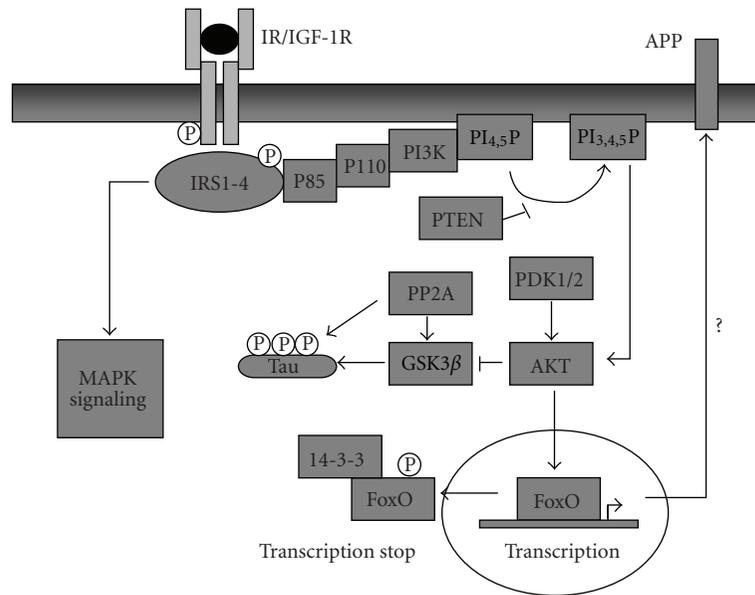


FIGURE 1: Central IR/IGF-1 signaling. Binding of insulin and IGF-1 to their receptors leads to autophosphorylation of the β -subunits of the IR or IGF-1R, recruitment of IRS-1/-2, and subsequently activation of mainly two pathways the PI3 kinase pathway and the MAP kinase cascade. The PI3 kinase pathway activates Akt which inhibits GSK-3 β . Akt-mediated FoxO1 phosphorylation results in binding of the regulatory protein 14-3-3 and nuclear exclusion of FoxO1. Abbreviations: IR, insulin receptor; IGF-1R, insulin-like growth factor-1 receptor; IRS, insulin receptor substrate; PI3K, PI3 kinase; FoxO1, forkhead-box protein O1; PDK, phosphatidylinositide-dependent kinase; p110/p85, catalytic/regulatory subunit of PI3K; PI_{3,4}P, phosphatidylinositide 3,4-diphosphate; PI_{3,4,5}P, phosphatidylinositide 3,4,5-triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome ten; 14-3-3, regulatory protein 14-3-3; PP2A, protein phosphatase 2A.

Target genes	FoxO	Function
p21	FoxO1, FoxO3a, FoxO4	Cell cycle
p27	FoxO1, FoxO3a, FoxO4	Cell cycle
Manganese superoxide dismutase	FoxO3a	Stress response
Catalase	FoxO3a	Stress response
Bim	FoxO3a	Apoptosis
Fas ligand	FoxO1, FoxO3a	Apoptosis
p53	FoxO3a	Apoptosis
Glucose-6-phosphatase	FoxO1	Metabolism
PGC1	FoxO1	Metabolism
Phosphoenolpyruvate carboxykinase	FoxO1	Metabolism
IR	FoxO1	Signaling
FoxO1	FoxO1, FoxO3a	Signaling
FoxO3a	FoxO1, FoxO3a	Signaling

FIGURE 2: Function and targets genes of FoxO transcription factors. Abbreviations: IR, insulin receptor; PGC1, peroxisome-proliferative-activated receptor- γ (PPAR γ) coactivator 1; BIM, Bcl2-interacting mediator of cell death; p21, cyclin-dependent kinase inhibitor 1 (review in [58]).

6. Expression of FoxO during Aging and High-Fat Diet

FoxO transcription factors show a distinct temporal and spatial expression pattern at least in the murine brain.

The analysis of FoxO expression in different regions of mouse brain up to 100 weeks of age revealed that FoxO1 is predominantly expressed in the hippocampus compared to overall expression in the whole brain, whereas FoxO3a showed its highest expression in the cerebellum [51]. Furthermore, expression of FoxOs in C57BL/6 mice strongly respond to a high-fat diet (HFD) at least if fed over 46 weeks. Western blot analysis of cortex lysates of these HFD mice revealed increased phosphorylation of AKT at Ser473 compared to mice on STD (standard diet) indicating increased IR/IGF-1 signaling in these mice. Surprisingly, FoxO1 mRNA levels were slightly increased in the CNS of HFD mice, whereas FoxO3a mRNA levels were significantly decreased in the cerebellum, frontal, parietal, and occipital cortex. Even more strikingly, the expression of FoxO6 was upto 80% decreased in all analyzed brain regions [51]. In line with these *in vivo* data, SH-SY5Y human neuroblastoma cells stably overexpressing IRS-2 showed increased phosphorylation of AKT at Ser473 and analysis of mRNA levels of FoxO3a revealed significantly reduced expression as observed in the CNS of mice fed a HFD indicating that chronically elevated IR/IGF-1 signaling in neurons leads to downregulation of FoxO3a *in vivo* and *in vitro* [51]. The exact molecular mechanism how IR/IGF-1R signaling cascade regulates expression of the different FoxOs is still under investigation. However, data obtained in cell lines might not exactly reflect the *in vivo* situation. Thus, hyperinsulinemia in mice fed a HFD over a long period induces decreased expression of FoxO transcription factors, for example, FoxO3a and FoxO6, suggesting that disturbance of FoxO-mediated transcription

FoxO		FoxO1	FoxO3a	FoxO4	FoxO6	Kinases
(P)		T24	T32	T28	T26	AKT/PKB SGK
(P)	FKH	S152- S155 S184				cGK1
(P)			S207			MST1
(P)		S249				CDK2
(P)	NLS	S256	S253	S193	S184	AKT/PKB SGK
(P)		S319	S315	S258		AKT/PKB SGK
(P)		S322 S325				CK1
(P)		S329				DYRK1
	NES					
(P)	TA			T447 T451		JNK
(P)			S644			IKK β
(P)						

FIGURE 3: FoxO phosphorylation sites regulated via different kinases. Abbreviations: PKB, protein kinase B/Akt; SGK, serum- and glucocorticoid-induced protein kinase; cGK, cGMP-dependent protein kinase type 1; MST1, mammalian sterile 20-like 1 kinase; CDK 2, cyclin-dependent kinase 2; CK1, casein kinase 1; DYRK, dual specificity tyrosine-phosphorylation-regulated kinase; JNK, c-Jun N-terminal kinase; IKK, I κ B-kinase, NLS, nuclear localization signal; NES, nuclear export signal; FKH, forkhead domain; TA, transactivation domain.

downstream of the insulin signaling pathway might be involved in the pathogenesis of obesity-associated cognitive dysfunction. The hypothesis is supported by animal experiments indicating a role for IRS-2-mediated signals for memory formation [77]. Mice harboring a brain-specific deletion of IRS-2 showed enhanced spatial working memory. Taken into account that decrease in IRS-2 signaling induces FoxO-mediated transcription, the assumption that decreased FoxO expression observed in HFD mice is involved in the pathogenesis of obesity-associated cognitive impairment seems reasonable or even likely. There is growing evidence that at least in AD IR/IGF-1 signaling is disturbed. Thus, IR/IGF-1-regulated transcription might be a part of the pathogenesis of at least AD. However, it is still unclear whether the changes in neuronal IR/IGF-1 signaling is cause or counterregulation in response to neurodegeneration.

7. Alzheimer’s Disease

Alzheimer’s disease is a chronic and progressive neurodegenerative disease. It is the most common form of dementia

leading to cognitive decline and death [78, 79]. Characteristics of AD are neurofibrillary tangles (NTFs) and β amyloid plaques. NTFs consist of hyperphosphorylated (abnormal high phosphorylation) tau proteins, and β amyloid plaques contain aggregated amyloid- β ($A\beta$) peptides [80, 81]. It is hypothesized that the accumulation of $A\beta$ is the leading cause for neurodegeneration in the progression of AD [80].

Several clinical studies showed that the IR/IGF-1R signaling is impaired in the central nervous system (CNS) of patients suffering from AD [82–84]. The expression of the IR and the IGF-1R was reduced in brains of AD patients [84, 85], whereas increased IGF-1 serum levels were detected [85, 86]. Additionally, the expression levels of IRS-1 and IRS-2 were reduced, and the inhibitory serine phosphorylation of IRS-1 at Ser312 and Ser616 was increased in AD brains. These findings indicate AD to be a brain type diabetes [87].

Tau predominantly occurs in the axons of neurons [88] and is less present in dendrites [89]. Tau might be involved in stabilization of microtubules and regulation of axonal transport [90]. It contains an N-terminal projection domain and a short tail sequence. The C-terminal domain consists of microtubule-binding (MTB) repeats. Tau gets phosphorylated at different sites by a variety of kinases. GSK3 β predominantly phosphorylates tau and is regulated via the IR/IGF-1R signaling pathway. Activated AKT phosphorylates Ser9 of GSK3 β to inhibit its action. An important phosphatase of tau is PP2A (protein phosphatase 2A) [91]. This phosphatase is also regulated via the IR/IGF-1R signaling cascade indicating that insulin and IGF-1 action promotes both phosphorylation and dephosphorylation leading to equilibrium of tau phosphorylation at least under certain circumstances [91, 92].

$A\beta$ peptides, the main component of amyloid plaques, are produced via proteolytic cleavage of the amyloid precursor protein (APP). APP belongs to the type-1 integral membrane protein family [93–96]. The APP gene is localized on chromosome 21, therefore patients suffering from trisomy 21 present an increased risk for AD. Hence, increased APP expression results in Alzheimer-like pathology [97, 98]. Furthermore, mutations in the APP gene itself like the Swedish mutation (APP^{sw}) or mutations in presenilin 1 and presenilin 2 which are involved in proteolytic cleavage of APP lead to familial early-onset AD (FAD) [99–107].

Different APP splicing variants with distinct molecular weight are generated *in vivo*. APP containing 751 or 770 amino acids (APP751 and APP770) is expressed in non-neuronal tissue, while APP695 is predominantly found in neurons [108]. The function of APP and APP-like protein (APLP) is not well understood. These proteins might be involved in apoptosis, axonal transport, and cell adhesion. APP and APLP are expressed in nearly all vertebrates and invertebrates [109–111]. The structure of APP consists of an N-terminal extracellular and a C-terminal domain located in the cytoplasm. Proteolytic cleavage of APP is promoted via the β -secretase BACE-1 (β -site APP cleaving enzyme) which leads to the “amyloidogenic pathway” of APP cleavage. APP is cleaved at Asp⁺¹ of the N-terminus via BACE-1 which leads to the generation of soluble APPs β and the C-terminal fragment C99 (Figure 4). C99 is cleaved via the γ -secretase,

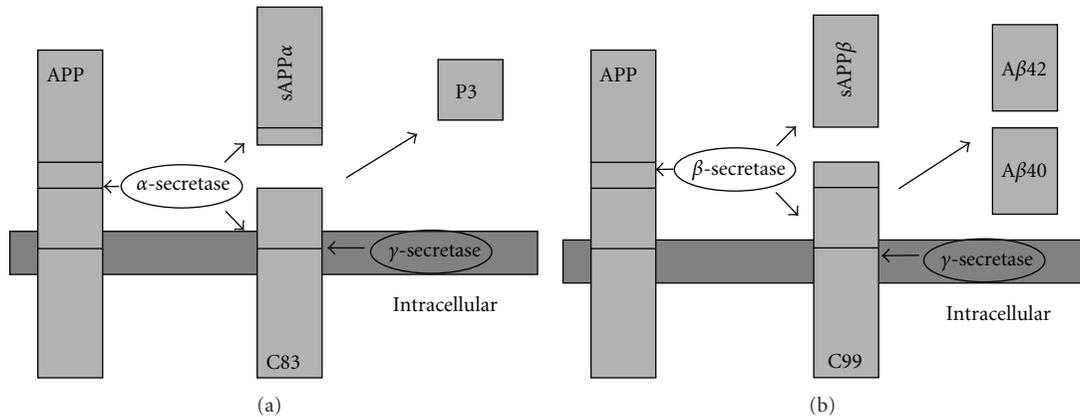


FIGURE 4: APP cleavage. (a) Nonamyloidogenic pathway: APP is cleaved by α -secretase leading to a membrane-bound C83 (α c-terminal fragment, α CTF) and the soluble APPs α ; (b) amyloidogenic pathway: APP is cleaved via the β -secretase (BACE-1) and γ -secretase (presenilin complex). β - and subsequent γ -cleavage of APP leads to generation of β -amyloid_{40/42}(A β). Abbreviations: APP, amyloid precursor protein; A β , β -amyloid; BACE, β -site cleavage enzyme.

a complex formed by presenilin, nicastrin, Aph-1, and Pen-2. This cleavage results in the production of A β (4 kDa) and the APP intracellular domain (AICD) with a size of 6 kDa. A β -peptides are mainly found in two variants which are distinguishable because of their size. A β 40 ends at residue 40 and A β 42 ends at residue 42. Predominantly, the A β 42 is susceptible to aggregate and forms neurotoxic oligomers. In contrast, the “nonamyloidogenic pathway” starts with cleavage of APP via the α -secretase ADAM10 (a disintegrin and metalloproteinase-like 10) or TACE (tumor necrosis factor- α convertase) which leads to the generation of the soluble APPs α and the C-terminal fragment C83. The decision whether the amyloidogenic or nonamyloidogenic cleavage pathway is induced depends on the competition of the α - and β -secretase [107, 110]. Up to 90% of all A β -peptides in brains of healthy people are A β 40, whereas A β 42 is less produced with about 5 to 10% [112]. The accumulation of A β 42 is a major step in the formation of A β oligomers amyloid plaques [113]. A β oligomers show an increased cytotoxic effect compared to mature A β fibrils [114–116]. A β -derived diffusible ligands (ADDLs) are aggregates with a size of about 17 to 42 kDa and present no fibrillar structure but are neurotoxic [117–119], and the concentrations of ADDLs correlate to cognitive impairment in AD [120].

The exact mechanism how A β facilitates its neurotoxic effect is not completely understood yet, but toxicity might be induced via generation of ion channels, membrane disruption, oxidative stress, induction of apoptosis, and inflammation [121–124].

8. Insulin/IGF-1 Signaling and FoxO-Mediated Transcription in the Pathogenesis of Alzheimer’s Disease

In cultured human neurons, Hong et al. [125] showed that glycogen synthase kinase-3 (GSK-3) phosphorylates the

neuronal protein tau. Hyperphosphorylated tau is the major component of paired helical filaments in neurofibrillary lesions associated with Alzheimer’s disease. Hyperphosphorylation reduces the affinity of tau for microtubules and is thought to be a critical event in the pathogenesis of tauopathies. Insulin and IGF-1 have been shown to reduce the phosphorylation of tau protein by inhibiting activity of GSK-3. *In vivo* IRS-2-deficient mice, a model of insulin resistance and type 2 diabetes, displayed tau-hyperphosphorylation and developed intracellular deposits of hyperphosphorylated tau during aging [126] suggesting a critical role for IR/IGF-1 signaling in regulation of tau phosphorylation *in vivo*.

Previous studies suggest that insulin and IGF-1 support neuronal survival *in vitro*. In particular, insulin/IGF-1 strongly activates AKT/PKB to promote BAD phosphorylation and its association with 14-3-3, which releases Bcl-2 to inhibit apoptosis [127]. Furthermore, IR/IGF-1-receptor signal transduction regulates the processing and secretion of APP [128, 129], and Xie et al. [129] have demonstrated that β -amyloid peptides compete for insulin’s binding to the IR. As mentioned above, IR/IGF-1R is reduced in AD brains strongly suggesting a role for IR/IGF-1 signaling in the pathogenesis of AD. This is supported by several animal models. For example, IGF-1-deficient mice presented increased tau phosphorylation at Ser396 and Ser202 [130]. The brain-specific knockout of the IR (NIRKO) showed highly phosphorylated tau at Thr231 [131]. IRS-2-deficient mice displayed “hyperphosphorylation” at Ser202 [126]. Thus, genetically induced IGF-1 or insulin resistance in mice induces tau hyperphosphorylation, indicating that at least the tau part of AD pathology is enhanced by insulin resistance *in vivo*.

In contrast, animal experiments suggest a different role of IR/IGF-1 signaling for the β amyloid pathology in AD. Tg2576 mice express the human-derived APP harboring the Swedish mutation (APP^{sw}) inducing increased A β burden and AD-like pathology [107, 132–135]. Mice with

a neuron-specific IGF-1R deletion (nIGF-1R^{-/-}) or IRS-2 knockout (IRS-2^{-/-}) crossed with Tg2576 mice were protected from premature death and showed decreased A β accumulation [136]. Interestingly, neuron-specific deletion of the IR (nIR^{-/-}) in a Tg2576 background showed decrease in A β burden but displayed no survival benefit compared to Tg2576 mice [137].

A rather interesting study investigated the role of partial IGF-1 resistance in an AD mouse model overexpressing APPsw and the human presenilin-1 Δ E9 variant under control of the prion promoter [138]. These AD mice were crossed with mice heterozygote for the IGF-1R (Igf1r^{+/-}). These APPsw and presenilin-1 Δ E9/Igf1r^{+/-} mice showed an increased assembly of A β into densely packed, fibrillar structures [139]. This so-called hyperaggregation suggests an active aggregation of highly toxic A β oligomers to densely packed aggregates which are less neurotoxic. In summary, this study suggests that partial IGF-1 resistance protects the brain from neurotoxicity mediated via A β oligomers [139].

In *Caenorhabditis elegans*, the knockdown of DAF-2, the ortholog of mammalian IR and IGF-1R using siRNA (small interference RNA) has been shown to reduce A β 42 toxicity [140]. This reduced toxicity was caused via the downstream transcription factor DAF-16 (Abnormal dauer formation 16), the ortholog of the mammalian FoxO1 and FoxO3a, and HSF-1 (heat shock transcription factor-1) [140–142]. HSF-1 induces disaggregation of the toxic A β oligomers and degradation. In case this mechanism is oversaturated, DAF-16 promotes the formation of hyperaggregated A β -peptides which leads to aggregates with high-molecular weight and less toxicity [140].

Recently, two mouse models expressing neuron-specifically a dominant negative or constitutive active form of FoxO1 (FoxO1DN and FoxO1ADA), have been published. The first mutant, FoxO1ADA, is nuclear expressed due to mutation of T24 and S316 to A as well as a mutation of S256 to D and acts constitutively active. The second FoxO1 mutant is transactivation domain deleted (FoxO1DN) and exerts a dominant negative effect. These mice were crossed with Tg2576 mice and analyzed in respect to survival, APP processing, and A β aggregation. FoxO1DN mice in a Tg2576 background showed no differences in survival up to 60 weeks of age compared to Tg2576 mice in both genders. Interestingly, FoxO1ADA mice which mimic the situation of an inactive IR/IGF-1R signaling pathway presented no differences in A β burden. However, these mice showed an increased mortality compared to Tg2576 mice for a yet unknown reason [137]. Thus, in mammals FoxO1-mediated transcription does not explain the beneficial effects mediated via the IR/IGF-1 pathway.

An alternative downstream candidate of the IR/IGF-1R signaling pathway is FoxO3a. Caloric restriction activates the IR signaling pathway resulting in phosphorylation of FoxO3a and nuclear exclusion [143]. A recent study showed that this inactivation of FoxO3a leads to attenuation of AD pathology and preservation of spatial memory in Tg2576 mice. Accordingly, *in vitro* studies using primary corticohippocampal Tg2567 neuron cultures expressing a constitutive active FoxO3a revealed increased A β -peptide

production. In addition, FoxO3a is deacetylated by SIRT1 which might result in inhibition of FoxO3a-mediated transcription during caloric restriction. This leads to reduced Rho-associated protein kinase-1 (ROCK1) gene expression followed by activation of the nonamyloidogenic processing of APP and decreased levels of A β -peptides [143]. Thus, animal experiments support the hypothesis that increased FoxO-mediated transcription does not protect but rather increase amyloid pathology.

The clearance of A β from the brain is facilitated via different mechanisms: (i) transport across the blood brain barrier (BBB), (ii) phagocytosis by microglia, and (iii) enzymatic degradation. Transport across the BBB is promoted via A β binding to the low-density lipoprotein receptor-related protein (LRP) directly or via its associates to LRP in complex with APOE (apolipoprotein E) and/or α 2-macroglobulin (α 2M). After crossing the BBB A β -peptides are delivered to peripheral tissues, for example, liver for degradation [144]. Previous studies proposed that IGF-1 plays an important role for degradation and clearance of A β . This was supported by the finding that Tg2576 mice have decreased IGF-1 levels in comparison to wild-type animals and that the treatment with IGF-1 causes an increased transport of A β out of the brain [145]. Thus, there might be a different role for IGF-1R signaling in neurons and serum IGF-1 levels acting on A β transport across the blood brain barrier. This point clearly needs further investigations.

Taken together, studies in humans have shown neuronal IR/IGF-1 resistance as being part of the pathogenesis of AD. However, there seems to be a dual role of IR/IGF-1 signaling in the pathogenesis of AD. Recent animal experiments indicate that central insulin and IGF-1 resistance is most likely a compensatory mechanism to β amyloid pathology to reduce A β toxicity and promote survival. But decreased IR/IGF-1 signaling causes tau hyperphosphorylation which is neurotoxic at least to certain extent. Experiments in *C. elegans* suggested that FoxO transcription factors might be involved in mediating the beneficial effects of reduced IR/IGF-1R signaling. However, studies in rodents favor that at least transgenically induced increased FoxO-mediated transcription might be harmful at least for AD pathology or AD-associated mortality, favoring a concept for the exigency of optimal balanced IR/IGF-1R \rightarrow FoxO-mediated transcription under disease conditions.

9. Alternative Targets Regulated by Insulin/IGF-1 Signaling Possibly Involved in Aging and Pathogenesis of Dementia

However, FoxO-mediated transcription is not the only target of the IR/IGF-1R signaling cascade. Alternative effectors downstream the IR/IGF-1R have been suggested as possibly being involved in the pathogenesis of dementia or aging itself.

The PI3K pathway leads to activation of AKT. In addition to phosphorylation of FoxO, it regulates tuberin 2 (TSC-2). TSC-1 and -2 form a heterodimer harboring GTPase

activity and inhibiting the GTPase RHEB (RAS homolog enriched in brain). Upon phosphorylation, the RHEB-GTP complex accumulates and leads to activation of mTOR (mammalian target of rapamycin) [146, 147]. Activated mTOR phosphorylates 4E-BP (4E binding protein) which then releases eIF4E (eukaryotic initiation factor 4E) promoting translation initiation. Furthermore, activated PDK1 and mTOR activate the S6 kinase (S6K). S6K phosphorylates eEF2 (eukaryotic elongation factor 2) kinase to release eEF2 which leads to initiation of elongation [148, 149]. Hence, the IR/IGF-1R signaling cascade increases protein synthesis in general. Recently, inhibition of mTOR using rapamycin has been shown to increase lifespan and age-dependent cognitive deficits in mice [150, 151]. At the moment, no data addressing the role of mTOR for the pathogenesis of AD are available, but this will be an interesting direction for further research.

The insulin/IGF-1 signaling cascade does not only regulate the PI3K pathway but also the MAP kinase (MAPK, mitogen-activated protein kinase) cascade. After activation of the insulin/IGF-1 signaling pathway, GRB-2 binds to phosphorylated IRS proteins [36]. After that, GRB-2 recruits son of sevenless (SOS), which is a GDP/GTP exchange factor. Then the activation of the small G-protein RAS results in association of c-raf leukemia viral oncogene (CRAF) to the membrane activating kinase (MAPK). Finally, the MAP kinases activate the extracellular signal-regulated kinase (ERK-1/-2) [46]. The activity of ERK-1/-2 has been shown to be involved in long-term potentiation and memory in the CNS [47]. Thus, the MAP-kinase pathway might be involved in certain aspects of the pathogenesis of dementia as well.

10. Conclusion

Obesity in midlife and type 2 diabetes are associated with an increased risk for vascular dementia and Alzheimer's disease. One common feature of obesity and type 2 diabetes is hyperinsulinemia leading to insulin desensitization. This has been identified at least as risk factor for cognitive decline. At least in AD, neuronal IR/IGF-1R signaling is severely impaired. Thus, reduced IR/IGF-1R signaling is part of the pathogenesis of AD. Interestingly, deletion of the IGF-1R in mouse models of AD leads to reduced mortality and decreased A β load. Furthermore, haploinsufficiency for the IGF-1R increased A β aggregation which is hypothesized to be a molecular mechanism of detoxification. Interestingly, neuron-specific deletion of the IR reduced the A β burden without influencing mortality. Thus, reduced IR/IGF-1R signaling observed in AD brains might be a compensatory mechanism protecting the brain against the toxic influence of chronic elevated insulin levels. Data obtained from *C. elegans* indicated that the FoxO transcription factors might mediate the beneficial effect induced via decreased IR/IGF-1 signaling. However, very recent data in rodents using transgenic expression of different FoxO variants nearly excludes FoxO1-induced transcription as mediators for these effects.

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Research Article

Dyslipidemia and Blood-Brain Barrier Integrity in Alzheimer's Disease

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Background. Blood-brain barrier (BBB) dysfunction may have a significant role in the pathogenesis of Alzheimer's disease (AD). Modifiable factors associated with BBB function may have therapeutic implication. This study tested the hypothesis that dyslipidemia is associated with BBB impairment in mild-to-moderate AD. **Methods.** Thirty-six subjects with AD were followed for 1 year. Fasting CSF and plasma were collected with clinical assessments at baseline and 12 months. BBB impairment was defined as CSF albumin index ≥ 9 . Independent *t*-tests and linear regression assessed the relationship between plasma lipoproteins and BBB integrity. **Results.** Dyslipidemia was prevalent in 47% of the population, and in 75% of those with BBB impairment. Subjects with BBB impairment had significantly higher mean plasma triglyceride and lower HDL cholesterol (TG, $P = 0.007$; HDL, $P = 0.043$). Plasma triglycerides explained 22% of the variance in BBB integrity and remained significant after controlling for age, gender, ApoE-4 genotype, blood pressure, and statin use. **Conclusion.** Dyslipidemia is more prevalent in AD subjects with BBB impairment. Plasma triglyceride and HDL cholesterol may have a role in maintaining BBB integrity in mild-to-moderate Alzheimer's disease.

1. Introduction

The CSF albumin index is an established measure of blood-brain barrier (BBB) integrity in living patients [1]. This index has detected a higher prevalence of BBB impairment in late onset dementia, including both Alzheimer's disease (AD) and vascular dementia compared to cognitively intact elders [2]. BBB impairment is associated with more rapid rate of decline in AD over 1 year [3]. Capillary endothelia dysfunction and the approximate tight junctions between these cells may be important to AD pathogenesis, including effects on maintaining cerebral perfusion and the clearance of toxic forms of beta-amyloid protein [4, 5]. The notion that the BBB is central to the pathogenesis of AD is controversial, but the enormity of the cerebrovascular tree and the similarity in risk factors between vascular and Alzheimer's disease makes the BBB and neurovascular unit difficult to disregard [6, 7].

If BBB function plays a role in the pathogenesis of AD, then modifiable factors associated with it may have therapeutic potential. A clinical trial of B vitamin supplementation has suggested that the BBB may be a modifiable entity in subjects with hyperhomocysteinemia and mild cognitive impairment [8]. Lipids are plausible candidates for modifying BBB function because of their relationship with vascular disease and ability to affect AD type pathology [9]. This study examines the relationship between dyslipidemia and BBB integrity in a well-characterized sample with mild-to-moderate Alzheimer's disease.

2. Methods

2.1. Study Population. The study participants were recruited from the clinic population of the NIA—Layton Aging and Alzheimer's Disease Center of Oregon Health and Science

TABLE 1: Study population characteristics¹.

	Total (<i>n</i> = 36)	BBB intact (<i>n</i> = 28)	BBB impaired (<i>n</i> = 8)
Age, years	70 (7.1)	70 (7)	73 (8)
Female, no. (%)	12 (33)	11 (39)	1 (13)
ApoE-ε4 allele carriers (%)	27 (75)	21 (75)	6 (75)
BMI (%)	27 (4.6)	26 (4)	29 (6)
BP, systole, mmHg	142 (23.2)	143 (21)	137 (30)
BP, diastole, mmHg	78 (12.2)	79 (13)	76 (8)
Mini mental state exam	19 (5.0)	20 (5)	18 (5)
Hachinski ischemia score	0.6 (0.9)	0.5 (0.8)	1.0 (1.3)
Statin use, no. (%)	8 (22)	5 (18)	3 (38)
Glucose, mg/dL	99 (18)	98 (18)	101 (17)
CSF albumin index	7.2 (3.7)	5.6 (1.7)	12.9 (3.3) ^{abc}
Atherogenic dyslipidemia, no. (%) ²	15 (42)	9 (32)	6 (75) ^a
Metabolic dyslipidemia, no. (%) ²	17 (47)	11 (39)	6 (75) ^a
Triglycerides, mg/dL	215 (132)	185 (86)	323 (204) ^{ab}
HDL cholesterol, mg/dL	48 (20)	52 (22)	35 (5) ^a
LDL cholesterol, mg/dL	129 (33)	132 (37)	120 (10)
Total cholesterol, mg/dL	216 (36)	218 (40)	210 (27)

BBB: blood-brain barrier, ApoE-ε4: apolipoprotein E epsilon 4, BMI: body mass index, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

¹Mean and standard deviation provided unless stated otherwise; ^a*P* < 0.05, ^{ab}*P* < 0.01, ^{abc}*P* < 0.001.

²Atherogenic dyslipidemia: triglycerides ≥ 150 mg/dL, LDL > 100 mg/dL and HDL < 50 mg/dL [15].

³Metabolic dyslipidemia: triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL [16].

University and have been described previously [3]. Briefly, all subjects had a consensus diagnosis of probable AD using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria and a Clinical Dementia Rating of 0.5 or 1 to establish disease stage of mild-to-moderate AD. All participants provided informed consent in accord with the Institutional Review Board for human study at Oregon Health and Science University. All subjects had CSF and blood available for analysis. Twenty-three of these 36 subjects have come to brain autopsy, and in all autopsy cases the clinical diagnosis of AD was confirmed pathologically.

2.2. Data Collection and Analysis. Thirty-six subjects with mild-to-moderate AD were evaluated by medical history, neurological and general examination, the Mini-Mental State Examination (MMSE) [10], the Clinical Dementia Rating scale (CDR) [11], the modified Hachinski ischemia score [12], and the Geriatric Depression Scale [13]. Cerebrospinal fluid and peripheral blood were collected, and brain MRI was performed.

Lumbar punctures were performed in the morning under standardized conditions at L3 to L4 or L4 to L5 interspaces, immediately aliquoted, and snap frozen at -70°C until assayed. These samples had normal cell count and glucose levels, and the aliquots analyzed were matched sequentially by draw to control for CSF content drift by sequence. A CSF-to-serum ratio of albumin (CSF Albumin Index) ≥ 9.0 was considered BBB impairment. Reproducibility of the CSF albumin index in AD over 1-year has been established

(intraclass correlation coefficient = .96) [3]. Blood samples collected at the same visit as CSF were analyzed for albumin, glucose, triglycerides, total cholesterol, and high- and low-density lipoproteins by standardized methods performed by the Atherosclerosis Lipid Research Laboratory at Oregon Health and Science University [14]. Laboratory staff was blind to all clinical covariates.

2.3. Statistical Analysis

2.3.1. Descriptive Analysis. Two sample *t*-tests compared the mean differences in CSF albumin Index by subjects classified as atherogenic dyslipidemia (triglycerides ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL and LDL cholesterol > 100 mg/dL [15]) and metabolic dyslipidemia (the atherogenic profile without reference to LDL cholesterol) [16]. Mean differences in each lipid were compared between subjects with and without BBB impairment.

2.3.2. Primary Analysis. Multivariable linear regression models were fit to assess the relationship between lipids and CSF albumin index by including potential confounders including age, gender, ApoE-4 genotype, blood pressure, and statin use. Alpha level for significance was set at 0.05 (2-tailed).

3. Results

Table 1 summarizes the study population. Blood-brain barrier (BBB) impairment was prevalent in 22%. Frequency of

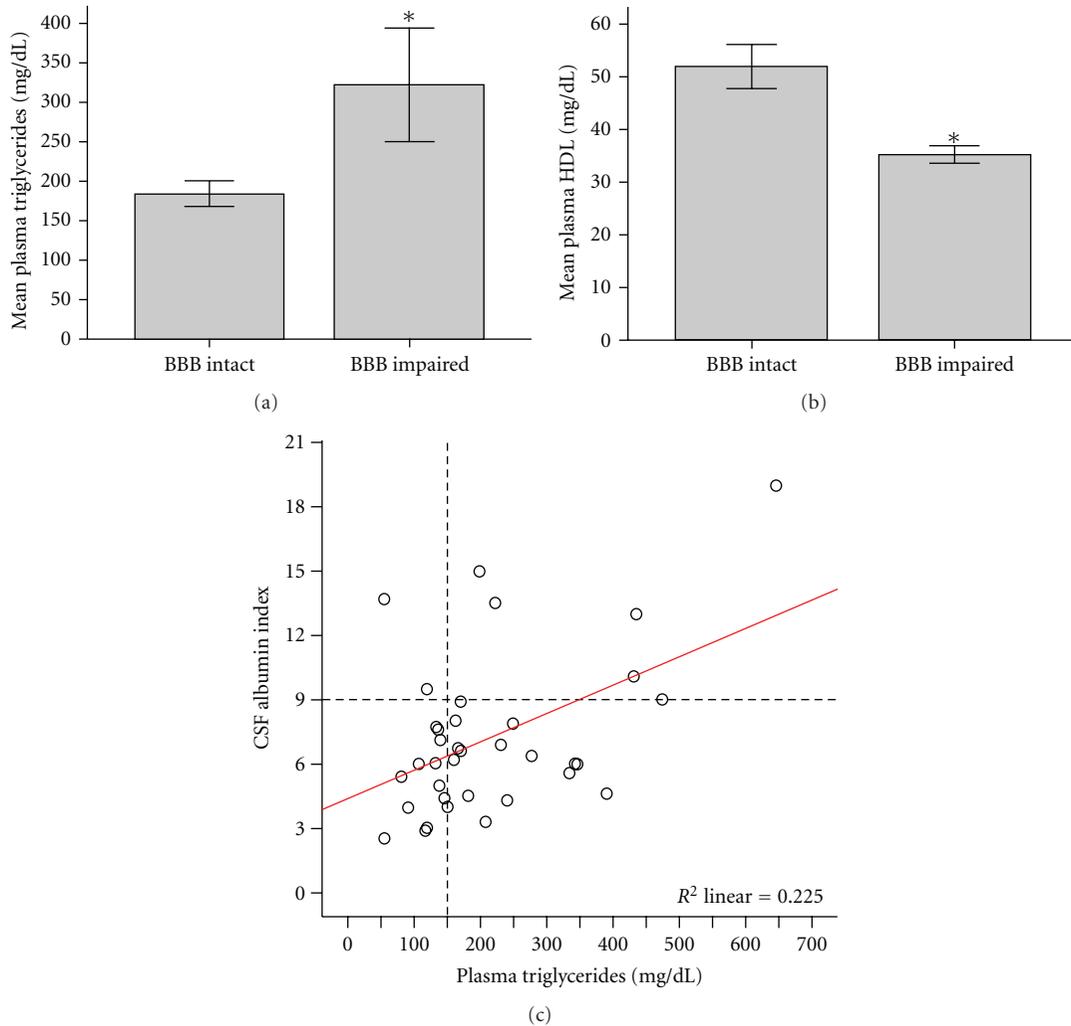


FIGURE 1: Relationship between plasma lipids and blood-brain barrier in subjects with AD. (a) Mean difference in TG = 137.89 mg/dL, $P = 0.007$. (b) Mean difference in HDL = 16.17 mg/dL, $P = 0.043$. Standard error bars around the mean set at ± 1.0 . (c) Horizontal reference line separates the plots by subjects with (above) and without (below) BBB impairment. Vertical reference line indicates lipid risk threshold.

statin use was similar between the groups with and without BBB impairment (P for difference = 0.251). Total and LDL cholesterol were not different between the two groups (total cholesterol, $P = .619$; LDL cholesterol, $P = .355$). However, mean plasma triglycerides were higher and HDL cholesterol lower in subjects with BBB impairment (mean difference in TG = 137.89 mg/dL, $P = 0.007$; mean difference in HDL = 16.17 mg/dL, $P = 0.043$) (Figures 1(a) and 1(b)). Seventy-five percent (6/8) with BBB impairment had plasma triglycerides ≥ 150 mg/dL (range 55–646 mg/dL) compared to 57% (16/28) in subjects with intact BBB (range 55–389 mg/dL). Everyone with BBB impairment had plasma HDL cholesterol below 50 mg/dL (range 29–43) compared to 60% (17/28) in subjects with intact BBB (range 23–106 mg/dL).

3.1. Dyslipidemia and BBB Impairment in Alzheimer’s Disease. The overall prevalence of “atherogenic” and “metabolic” dyslipidemia was 42% and 47%, respectively. The prevalence

of atherogenic dyslipidemia was more frequent in AD subjects with BBB impairment than in subjects without (75% versus 32% with intact BBB, $P = 0.030$, Table 1). Metabolic dyslipidemia was also more prevalent in BBB impaired (75% versus 39% with intact BBB, $P = 0.048$). Subjects with atherogenic dyslipidemia ($n = 15$) had mean CSF Albumin Index 2.69 units higher than those without ($n = 21$) ($P = .029$). Subjects with metabolic dyslipidemia ($n = 17$) had mean CSF Albumin Index 2.43 units higher than those without ($n = 19$) ($P = 0.48$).

3.2. Lipids Associated with BBB Integrity in Alzheimer’s Disease. Linear regression analysis indicated that each 10 mg/dL increase in plasma triglyceride content was associated with a 0.13 unit increase in CSF Albumin Index ($P = 0.004$) (Figure 1(c)). Plasma triglycerides explained 22.5% of the variation in BBB integrity. The association between plasma triglycerides and CSF Albumin Index remained significant in

multivariable regression analysis controlled for age, gender, ApoE-4 carrier status, systolic blood pressure, and statin use ($P = 0.040$). Total cholesterol, LDL cholesterol, and HDL cholesterol were not associated with CSF Albumin Index in the regression model (data not shown).

4. Conclusion

These findings demonstrate a higher prevalence of dyslipidemia in Alzheimer's subjects with BBB impairment. Plasma triglycerides and HDL cholesterol were the lipids most associated with BBB integrity. Plasma triglycerides explain the most variation in BBB integrity compared to HDL, LDL, and total cholesterol.

A relationship between triglycerides and dementia has been reported in one large study [17]. This group compared the various lipid components contributing to dementia risk but did not report data on BBB integrity. To our knowledge, this is the first study to report a significant relationship between dyslipidemia and BBB integrity in Alzheimer's disease. While a causal relationship between plasma lipids and BBB cannot be assumed, the most plausible explanation may be that BBB integrity in AD detected by the CSF Albumin Index is related to atherosclerosis and its risk factors. For example, the omega 3 polyunsaturated fatty acids, eicosapentaenoic acid, and docosahexaenoic acid are associated with both vascular disease and dementia risk and are known to lower plasma triglyceride levels [18]. It is also plausible that the effect of dyslipidemia on the BBB is independent of atherosclerosis. This has been observed in the case of an inborn error of cholesterol metabolism with neurologic complications, cerebrotendinous xanthomatosis [19].

Although sample size in this study is a limitation, we believe that the study has particular strengths worth noting. Sixty four percent of this study population has autopsy confirmed AD, and the entire sample had probable AD confirmed by consensus diagnosis. Another strength is the stability of the CSF Albumin Index as a measure of BBB integrity in living subjects [3] and the collection of fasting blood for the analysis of plasma lipids. These attributes minimize both risk of exposure and outcome misclassification and therefore strengthen the validity of the study findings in a limited sample.

The possibility that dyslipidemia is causally related to BBB impairment may be clinically significant since dyslipidemia is treatable. If this evidence is confirmed in other populations, then the next step may involve a lipid-modifying strategy to modify the natural history of AD. While it is true that statin therapy has been unsuccessful in altering the course of AD, these current findings place emphasis on modifying triglyceride and HDL cholesterol, ideally in subjects selected on the basis of BBB impairment at baseline. Perhaps a dietary pattern or supplementation with omega-3 PUFAs and niacin would offer one strategy, since they favorably modify triglyceride and HDL cholesterol metabolism, respectively [20]. The emergence of imaging modalities for the assessment of BBB integrity will make these types of intervention more feasible.

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Review Article

Nutrition in Severe Dementia

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An increasing proportion of older adults with Alzheimer's disease or other dementias are now surviving to more advanced stages of the illness. Advanced dementia is associated with feeding problems, including difficulty in swallowing and respiratory diseases. Patients become incompetent to make decisions. As a result, complex situations may arise in which physicians and families decide whether artificial nutrition and hydration (ANH) is likely to be beneficial for the patient. The objective of this paper is to present methods for evaluating the nutritional status of patients with severe dementia as well as measures for the treatment of nutritional disorders, the use of vitamin and mineral supplementation, and indications for ANH and pharmacological therapy.

1. Introduction

Dementia is one of the most common and most significant health problems in the elderly and is one of the main causes of disability in older age [1]. A growing proportion of older adults with Alzheimer disease (AD) or other dementias are now surviving to more advanced stages of the illness [2, 3].

Much clinical attention and research effort has been directed towards early diagnosis and mild stages of dementia, and prodromal stages, formerly classified as mild cognitive impairment (MCI). The later stages of the disease are as important as, if not more important than, the earlier stages because of the unique characteristics and events which occur affecting the lives of patients and their carers. Severe dementia (SD) is still relatively neglected and its prevalence is unclear, but it is estimated that one-third of dementia patients are in the severe stages [4–6].

There are several causes for concern in SD, when many impairments become more apparent: functional disabilities mean that carers have to take over more practical tasks, such as bathing, toileting, and feeding; there are special considerations with palliative care and ethical issues of terminal care along with physical problems [7–9].

SD, including AD, is associated with feeding problems, including difficulty in swallowing, leading to choking,

chewing but failing to swallow, and active resistance to hand feeding. Because patients with dementia have limited language and communication abilities, it is difficult to identify the source of aversive behavior [9, 10]. Nevertheless eating and drinking may well be a sensory pleasure for people with SD. That potential source of pleasure should be maximized while at the same time ensuring optimum nutrition and hydration [11].

In addition, weight loss is a frequent complication of AD and occurs in patients at all stages, even in the early stages before diagnosis is possible. Malnutrition (namely, undernutrition) contributes to the alteration of general health status, to the frequency and gravity of complications, especially infections, and to a faster loss of independence. These states of malnutrition can be prevented or at least improved if an early intervention strategy is set up, but management must be rapid and appropriate. Weight loss is a phenomenon whose kinetics may vary; it can be a dramatic loss of several kilograms in a few months (severe weight loss) or a moderate but continuous loss as the disease progresses (progressive weight loss) [12, 13].

With progressive dementia, patients become incompetent to make decisions. As a result, complex situations may arise in which physicians and families decide whether artificial nutrition and hydration (ANH) is likely to be

beneficial for the patient [14–16]. Many people with SD will ultimately experience dysphagia, which in turn is associated with aspiration pneumonia. Decisions about how to respond when someone develops swallowing problems are discussed elsewhere in this paper [17].

Artificial nutrition is the provision of liquid nutritional supplement by the enteral or parenteral route. The decision whether or not to provide artificial nutrition often evokes a powerful emotional response. Because surrogates and other loved ones agonize over the withholding and/or withdrawal of artificial nutrition, healthcare providers need to be ready to discuss the most current data regarding efficacy, complications, and the ethical and legal issues [18–20].

2. Definition of Severe Dementia

SD can be defined as the stage of the disease process of dementia in which cognitive deficits are of sufficient magnitude as to impair an otherwise healthy person's ability to independently perform the basic activities of daily life, such as dressing, bathing, and toileting. Definitions of SD vary from those which use a specific cutoff on a cognitive scale such as the Mini Mental State Examination. In accordance with the literature, we defined SD as follows [4]:

- (i) score of less than 10 in the Mini Mental State Examination (MMSE) [21] or
- (ii) score of 3 or higher in the Clinical Dementia Rating (CDR) [22], or
- (iii) categories 6a to 7f in the Functional Assessment Staging Test (FAST) [23], or
- (iv) score of 6 or 7 on the Global Deterioration Scale (GDS) [24].

Some investigators state that the incorporation of these instruments into clinical trials has allowed the rate of worsening or improvement of patients to be quantified in advanced stages. Moreover, they have permitted better stratification of this long stage known as SD, which includes patients with very different cognitive, behavioral, and functional profiles. Thus, among patients classified as CDR 3, known as SD, there are individuals who still communicate verbally and walk without support, but also others who are confined to bed, unable to lift their heads, or already in the fetal position. The advantages of better classification of advanced dementia include the possibility of better studies designed to validate interventions in cognition, behavioral, and functional status, as well as better approaches in terminal dementia using palliative care [5, 25].

Although by definition the functional impairment in dementia must be related to the cognitive decline, there are a number of other factors such as parkinsonism and comorbid disorders that by themselves contribute significantly to the functional disability [26].

So, unlike the dying trajectory in more-acute illnesses, patients with dementia have a long period of severe functional and cognitive impairment before death [27].

3. Nutritional Evaluation of Patients with Advanced Dementia

Cachexia and weight loss are common signs among AD patients. These findings have been studied to see if there is any correlation between organic deficiency caused by low-energy intake and the acute state of hypercatabolism these patients present. Undernourishment has been suggested to be a factor in the etiology of dementia and other psychiatric, and cognitive disorders, although nothing has been proven in this respect [28, 29].

Weight loss in AD may be correlated to the presence of higher rates of infection, the burning of energy due to repetitive movements and cognitive deficit that compromises the patient's independence [30, 31].

This process increases the risk of infections, skin ulcers and stimulates loss of body temperature, which consequently compromises the quality of life of patients with AD [32].

There is a theory behind the weight loss seen in AD patients that is based on the morphology and that has to do with the brain lesions caused by the disease, and a significant association has been found between low body weight and atrophy of the mesial temporal cortex in the region of the central nervous system responsible for eating behavior [33].

Guérin et al. [12] observed two forms of weight loss, one slow and progressive, the other rapid and severe. A severe weight loss was related to the seriousness of the disease, the higher number of hospital admissions, clinical events, and institutionalization, which led the researchers to conclude that these patients might benefit from nutritional interventions.

Munõz et al. [34] found that there is impairment of the energy and muscle reserves at all stages of the disease, but that there is a greater impairment of the Body Mass Index (BMI), and brachial fatty and lean mass, in the advanced stage.

Given these findings, evaluation of their nutritional status is crucially important for these patients. The result of the nutritional evaluation will guide the management to be followed in each case.

The nutritional evaluation of these patients may be carried out using a number of traditional methods based on objective evaluations such as anthropometry, the evaluation of clinical signs that are indicative of malnutrition, evaluation of food intake, the subjective Mini Nutritional Assessment (MNA), and by NSI-Nutrition Screening Initiative [35].

The MNA was developed in order to assess the risk of malnutrition in the elderly and identify those who could benefit from early intervention. This evaluation is made of 18 items including: anthropometry, nutritional evaluation, global clinical evaluation and self-perception of health, and may be used both in screening and to evaluate the nutritional status; any trained health professional can apply it [36].

The NSI is a self-applied questionnaire made up of 10 questions, created in order to assess primary health care; however, its use is not widely recommended since it has shown limited power of prediction for mortality in the elderly [37].

Most authors, despite these methods, consider the use of anthropometrical measurements to be the gold standard for nutritional evaluation, along with outpatient tests for total lymphocytes, albumin, blood cholesterol, hemoglobin, and transferrin [38].

A nutritional evaluation study made in a long-stay institution with dementia syndrome, depression, and cardiovascular diseases, using anthropometric data gathering, found that 36.6% of these patients were malnourished, demonstrating the importance of early nutritional intervention [39].

Spaccavento et al. [13], using MNA to investigate the role of the nutritional status, correlating it to cognitive, functional, and neuropsychiatric deficits in AD patients, found that patients at risk of malnutrition showed greater impairment, both in simple instrumental daily life activities (DLA and IDLA) and a greater likelihood of presenting hallucinations, apathy, aberrant and nocturnal motor behavior on the sub-scales of the Neuropsychiatric Index (NPI).

Weight loss has a negative impact on the prognosis of AD since the more severe the malnutrition is the faster will be the clinical progression leading to the death of patients [40].

4. Nutritional Management of Patients with Advanced Dementia

4.1. Does Oral Nutritional Therapy (ONT) in Patients with Advanced Dementia Bring Benefit for the Nutritional Status? In patients with advanced dementia there is a reduced capacity for communication, loss of pleasure in eating, changes in mastication leading to difficulty in swallowing certain consistencies of food, and culminating in dysphagia [41].

These patients tend to present reduced mobility leading to loss of muscle mass even when not malnourished. In these cases nutritional therapy plays an essential role since it aims to provide comfort in the eating process and assure the patient's dignity [31].

As AD advances, the difficulty of keeping these patients' weight up through conventional feeding increases, and in these cases it is recommended to use high-calorie concentrates [42].

ESPEN, the European Society for Clinical Nutrition and Metabolism [43], classifies as evidence level C the use of dietary supplements to maintain the nutritional status of patients with dementia.

Pivi et al. [44], in their study of oral nutritional therapy with patients at different stages of AD, found that an additional 690 kcal/day in these patients' diets led to an improvement of the nutritional indices BMI, BC (brachial circumference), BMC (brachial muscle circumference), and TLC (total lymphocyte count), demonstrating that nutritional supplementation is in fact effective at any stage of the disease.

Carver and Dobson [45] likewise found that dietary supplementation significantly increases body weight, tricipital skin fold, and brachial muscle circumference in hospitalized elderly dementia patients.

Although dietary supplementation shows benefits for nutritional status, only 11% of outpatients use them, as

a study by Trelis and López [46] showed. This study highlighted the importance of the entire team involved in the treatment of dementia patients being able to perceive the onset of nutritional deficit and so refer the patient to the nutritionist to indicate the best type of supplement for each case.

Other studies with nondemented elderly patients with other clinical needs also showed the effectiveness of using dietary supplements in addition to the habitual diet. Volkert et al. [47] showed that elderly patients over 75 who were given calorific supplementation of 500 kcal/day improved their convalescence and recovery from deficiency states.

It is important to mention that there are lines of research that recommend the prescription of dietary supplements only for patients with low BMIs, since they may abandon their habitual diets in favor of dietary supplements [48].

Young et al. [49] also demonstrated this concern in a study with use of dietary supplements for 21 days in addition to their habitual diets. Those patients who received nutritional supplements were observed to have less likelihood of increasing energy intake in their habitual diets. The researchers stressed out that patients with low body weight have a greater chance of benefitting from the use of nutritional supplements.

This whole discussion leads us to observe that a natural diet ingested by mouth promotes patient comfort and dignity and may not shorten survival, since there are reports of patients who survived two years exclusively feeding by mouth [31]. There is evidence that dietary supplementation may enhance the nutritional status of dementia patients, regardless of the phase at which they are. The significance of this nutritional improvement has yet to be determined for the rate of cognitive and functional decline.

5. Use of Vitamins and Minerals in Alzheimer's Patients

No specific or definitive environmental risk factor has been identified as the likely cause of AD, but there are research lines that correlate diet as a preventive and improving factor for the dementia states.

There is evidence of worsening of the cognitive condition linked to the increase of homocysteine, whereas the consumption of fats and red grapes seems to have a protective effect for AD patients [50].

De Jong et al. [51] studied patients who followed dietary instructions and consumed foods supplemented daily with 0.25 mg of folic acid and 2.5 mg B6 vitamin; they found that these participants showed a reduction in the serum concentration of homocysteine of around 25%. This result suggests that a low concentration of homocysteine may inhibit the development of dementia.

Morris et al. [52] studied nurses who consumed polyunsaturated fatty acids at least once a week; although results were not conclusive, they suggested that this cohort had a lower risk of developing AD.

Polyphenols, in particular resveratrol, found in great quantities in red grapes, are believed to reduce the incidence

of AD owing to their antioxidant properties, although this has not yet been proved [53, 54].

A study of supplementation with low concentration of folic acid and B vitamin complex were made to investigate the association of these substances with enhanced cognitive function. It raised the prospect of reduction of dementia risk, but researchers emphasized that more studies are needed to prove this [55].

Study with AD patients in the mild phase who received micronutrient supplementation for six months found that, when compared to the control group, there was no benefit in the supplementation for the evolution of the disease, the nutritional status, the biochemical parameters, the cognitive function, and the behavior and eating disorders that these patients commonly present [56].

Despite the evidences, caution must be taken in adopting such approaches, since more studies on micronutrient supplementation need to be performed in order to observe real benefits for dementia.

6. Indication of Artificial Nutrition and Hydration in Advanced Dementia Patients

The use of Enteral Nutrition Therapy (ENT) or Artificial Nutrition and Hydration (ANH) is only indicated when there is a risk of malnutrition and severe impairment of the swallowing process, with the possible consequence of aspiration pneumonia [57].

According to ASPEN—American Society for Parenteral and Enteral Nutrition [58], an ENT in patients with advanced dementia is classified as category E, not obligatory in those cases. The decision for ENT must be based on effective communication with the caregivers to decide whether it should be used or not.

The use of nasogastric or nasoenteric tubes in patients with dementia is not recommended as they may pull out the tube, leading to discomfort for patient and family both, since the patient will have to be reintubated [59]. Gastrostomy is normally indicated as the route for alternative feeding, since it is already commonplace and laid down in rules when the duration of ENT is over six weeks [60].

ANH using feeding tubes or gastrostomy has been routinely indicated for patients in advanced stage of dementia who present serious problems swallowing, in order to prevent malnutrition, hydrate the patient properly, and provide comfort. Some studies, however, have put forward issues for the nonuse of ANH in these patients [59].

See Table 1 setting out the major studies in this field and their recommendations regarding ANH in advanced dementia patients:

The use of ANH in patients with dementia is very controversial being necessary identification of the goals for an intelligent and rational judgment [65].

Deciding whether to use ANH in dementia patients is a challenge and many caregivers may take their decisions without adequate information and based on an over-optimistic view of the future clinical course of this patient. Health professionals, relatives, and patients should be aware

of the realistic expectations of tube feeding and of its risks and benefits before taking such a decision [18].

Ethical dilemmas are related to ANH and it is useful in cases of severe dementia, being necessary to make valid clinical judgments and to guide patients and their families to exchange options related to initiating, withholding, or withdrawing ANH. All this process should be comprehensive and understood from theory to practice. The use of informed consent for competent caregivers is important in those cases [66].

7. Pharmacologic Therapies

Several randomized controlled trials have been published on atypical antipsychotic therapy for behavioral and psychological symptoms in patients with SD.

Some results suggested no significant difference between any of the treatments compared with placebo. They also support the recommendation for the use of atypical antipsychotics only in the presence of severe agitation, aggression, or psychosis that places the patient or those in their environment at risk. Other psychotropic drugs include the antidepressants and anticonvulsants. On balance, the efficacy of the atypical antipsychotics appears to be superior to that of other classes of drugs despite the increased risks. However, there are few, if any, head-to-head comparisons to truly characterize all risks and benefits [7]. In a meta-analysis adverse events of atypical antipsychotics were mainly somnolence and urinary tract infection or incontinence across drugs, and extrapyramidal symptoms or abnormal gait were observed with risperidone or olanzapine. There was no evidence for increased injury, falls, or syncope. But there was a significant risk for cerebrovascular events, especially with risperidone [67]. With all these studies it is possible to imagine that management of behavioral disorders could improve nutritional status. We also know that some antipsychotic drugs could improve appetite, and we could use these drugs to improve food intake. But more studies are needed to better assess clinical significance and effectiveness of these hypotheses.

Pharmacological therapies for the improvement of cognition include cholinesterase inhibitors and memantine, suggesting that this class of medication improves cognition, function, behavior, and global measures. There is a consensus to recommend their use in patients with severe Alzheimer's disease.

The most common side effects are gastrointestinal and include anorexia, nausea, vomiting, and diarrhea [7]. It is therefore very important to pay attention to these problems so as not to impair food intake. There are no studies in the literature to demonstrate whether cholinesterase inhibitors or memantine could improve the nutritional status.

It is also important to register that there are no well-designed randomized studies to demonstrate benefits of appetite stimulant drugs. We know that it is common medical practice, but evidence of the mechanisms, safety, and efficacy is lacking.

TABLE 1: Results of the main studies in artificial nutrition and hydration (ANH) in patients with severe dementia.

Study	Objective and methodology	Results	Conclusion
Ciocon et al. [61]	Evaluate the indications, benefits, and complications of ANH in patients using enteral tube, with serious swallowing disorders and at risk of aspiration	67% of patients were agitated when the tube was removed and 43% had aspiration pneumonia during the study	Researchers concluded that the use of ANH may lead to a high frequency of complications
Finucane et al. [10]	Review of the literature (1966 to 1999) to evaluate the use of ANH in advanced dementia	No data to suggest that the use of ANH may prevent aspiration pneumonia, reduce the risk of infections or prolong life	Most studies show that there are substantial risks in using ANH in these patients, and thus its use is discouraged
Li [62]	Review the use of ANH in patients with advanced dementia	ANH does not prevent malnutrition, reduce the occurrence of bed sores, or prevent aspiration pneumonia, nor does it prolong life	Although it may not be effective in preventing malnutrition and dehydration, this type of feeding allows a degree of maintenance and patient comfort
Pasman et al. [19]	Evaluate the discomfort of patients with serious dementia of a Dutch nursing home	The highest rates of discomfort observed in these patients were in dyspnea, acute pain, and agitation	Not choosing ANH did not correlate with the level of discomfort of the patients. ANH was identified as an individual decision
Clarfield et al. [63]	Evaluate the use of ANH in patients with advanced dementia admitted to Israeli and Canadian hospitals in order to find the main differences between ethnicities and ethical issues	24,5% patients were in if fed by ANH	These results may be explained by a combination of administrative or financial incentives and by religion and culture
Volkert et al. [43]	ESPEN Guideline developed to recommend use of ONT or ANH in elderly patients based on scientific evidence	No increase in survival associated with this use, leading the researchers to consider ANH only according to patient's or family's wishes	ANH not recommended in patients with advanced dementia
Buiting et al. [64]	To investigate the opinion of Dutch and Australian physicians on use of ANH in patients with advanced dementia	Dutch physicians based their decision on a wide-ranging evaluation, while Australian physicians tended to use scientific evidence	All are reluctant at beginning of ANH but Dutch physicians tend to take primary responsibility for the decision, while Australian physicians prefer to leave the decision to the family

8. Final Remarks

There have been studies to develop drugs and treatments to understand nonpharmacological measures, to find epidemiological factors that affect the natural history of this disease, but they are not conclusive to define ways to approach the end of life or to look into issues such as suitable nutrition for these patients. The long drawn-out course and uncertain time frame of the prognosis raise considerable doubts as to decisions to be taken by the team of carers and by the relatives.

This paper demonstrates the palliative care that should be given in order to improve the patient's quality of life. All aspects of the treatment of these patients should therefore be part of the responsibilities of the multiprofessional team. It should act cohesively to help relatives take the best decisions in choosing treatment for their loved ones.

This view of comfort and of the right proportions between actions taken and the principle of nonharm may

serve as a guide in decision making, especially as regards nutrition issues [8].

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Research Article

Sarcopenic Obesity and Cognitive Functioning: The Mediating Roles of Insulin Resistance and Inflammation?

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This study examined the influence of insulin resistance and inflammation on the association between body composition and cognitive performance in older adults, aged 60–69 and aged 70 and older. Subjects included 1127 adults from NHANES 1999–2002. Body composition was categorized based on measurements of muscle mass and waist circumference as sarcopenic nonobese, nonsarcopenic obese, sarcopenic obese, and normal. Using OLS regression models, our findings suggest body composition is not associated with cognitive functioning in adults ages 60–69; however, for adults aged 70 and over, sarcopenia and obesity, either independently or concurrently, were associated with worse cognitive functioning relative to non-sarcopenic non-obese older adults. Furthermore, insulin resistance accounted for a significant proportion of the relationship between cognitive performance and obesity, with or without sarcopenia. Additionally, although high CRP was significantly associated with poorer cognitive functioning in adults ages 60–69, it did not influence the association between body composition and cognitive performance. This study provides evidence that age-related physiological maladaptations, such as metabolic deregulation, which are associated with abdominal fat, may simultaneously contribute to lower cognition and muscle mass, reflecting a degradation of multiple physiological systems.

1. Introduction

Both obesity and frailty or underweight status have been identified as important risk factors for poor cognitive functioning among older adults. White matter lesions and cerebral atrophy have been found to be more common in adults with a high body mass index (BMI) [1, 2], and midlife measures of central obesity have been found to predict poor performance on tests measuring executive functioning and visuomotor skills [3]. It is also true that being underweight or frail may be linked to cognitive performance. Sturman et al. found a curvilinear association between BMI and cognition at baseline; however, after 6 years, subjects who were underweight experienced greater cognitive decline than normal weight subjects, while obese subjects did not have significant declines in cognition [4]. Given that the impact of body composition is not fully understood, more research is needed to further uncover the mechanisms driving the association. Furthermore, little information currently exists regarding

the confluence of body composition phenotypes and the physiological mechanisms which directly or indirectly affect cognitive performance.

As individuals age, increases in fat mass are hypothesized to stem from reductions in physical activity and retained caloric intake levels in the presence of a declining basal metabolic rate [5]. Concurrently, many individuals also experience significant declines in muscle mass and strength with aging, referred to as sarcopenia [6–8]. Age-related changes in muscle mass and adiposity may stem from a mutual pathophysiological mechanism. It has been proposed that systemic inflammation and insulin resistance may play a part in the concurrence of abdominal obesity and sarcopenia. Proinflammatory cytokines are synthesized and secreted by adipocytes [9] and may promote the breakdown of skeletal muscle fiber diameter and protein content, as well as disrupt muscle force production and fatigue resistance [10]. Additionally, insulin resistance, which is often observed in subjects with excess visceral adiposity, due to increases

in cytokine production [11], is believed to contribute to metabolic deterioration of skeletal muscle, manifesting clinically as sarcopenia [12].

Age-related alterations in inflammation and insulin resistance may also have implications for cognitive functioning and may partially explain the associations between poor cognitive performance and body composition. Systemic inflammation has been identified as a potential risk factor for cognitive impairment. In cross-sectional studies, increased levels of CRP were associated with lower levels of executive functioning and global cognition [13]. Furthermore, longitudinal studies have provided evidence that high levels of CRP and IL-6 may accelerate the rate of cognitive impairment for high functioning older adults [14]. Poor cognitive functioning has also been associated with disruptions in metabolic processing. The importance of the insulin-signaling pathway has been identified as a factor facilitating the maintenance of cognitive functioning ability. Furthermore, higher insulin resistance, as measured using the homeostasis model of assessment (IR_{HOMA}), has been found to be associated with poorer cognitive efficiency and poorer visual scanning with added cognitive flexibility [15].

Insulin resistance, inflammation, cognitive functioning, and body composition are strongly linked to aging and may represent an age-related decline in multiple physiological systems. Our study examines a nationally representative sample of community-dwelling US citizens over the age of 60 to determine whether insulin resistance and inflammation partially account for the associations between cognitive functioning and body composition. Because the variables being examined are closely linked to age [16, 17], our analysis is run for two separate cohorts, in order to investigate whether the influence is different at various stages of old age. Furthermore, to more precisely study the association between cognitive performance and a diverse spectrum of body types related to changes with age, we examine body composition as a combination of abdominal adiposity and muscle mass to facilitate our ability to examine an interaction between obesity and frailty. Based on previous research, we hypothesize that individuals who are sarcopenic obese will have lower cognitive ability than nonsarcopenic nonobese subjects and that this association will be explained, in part, by high levels of insulin resistance and CRP. Furthermore, because cognitive functioning, body composition, and physiological health deteriorate with age, we hypothesize that these associations will be stronger among subjects aged 70 and over, as compared to subjects aged 60–69.

2. Materials and Methods

2.1. Study Population. The study population was comprised of males and females aged 60 and older from two subsamples of the US National Health and Nutrition Examination Survey (NHANES 1999–2002)—a nationally representative, cross-sectional study conducted by the National Center for Health Statistics (NCHS) [18]. Data were collected during at-home interviews and at clinical and laboratory examinations, taking place at a Mobile Examination Center (MEC). Anthropometric data measurements for body composition were

measured by dual X-ray absorptiometry (DXA). Because of the potential for nonresponse bias in the use of only cases with information from the DXA scans, imputed data were utilized in analysis as developed and recommended by NHANES [18]. The NHANES files contain five sets of imputed data for each eligible participant with missing DXA data. While only one record was used in calculating sample sizes, all five records were used in analyses to insure more accurate variance estimates were obtained.

The total subsample size for eligible participants over age 60 from both NHANES 1999–2000 and 2001–2002 was 1630. Due to missing data from the examination and laboratory tests, those who were included in the study were 70% ($N = 1127$) of the original subsample, of whom 555 were aged 60–69 and 572 were aged 70 and over. The subsample included individuals who were tested for plasma glucose in a morning laboratory exam and who had fasted for eight to twelve hours before. Because individuals with diagnosed diabetes were not asked to fast, those individuals were excluded from the study. Further details of recruitment, procedures, and study design are available through the U.S. Department of Health and Human Services [18].

2.2. Cognitive Functioning. Cognitive functioning was based on the score for the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Digit Symbol-Coding module administered during the household interview. Scores are based on the number of correctly drawn symbols, out of 133, within a 120-second period. Subjects who were unable to complete the cognitive performance task without assistance were not given scores and, therefore, not included in our analysis. The scale is considered to be a more precise indicator of diminished cognitive skills than the Minimalist Status Exam and has been administered in the Health ABC study from the National Institute on Aging [18].

2.3. Body Composition. Body composition measurements included waist circumference, weight, height, and skeletal muscle mass (SMM). Body weight was measured using standardized procedures and equipment and was recorded to the nearest 0.01 kg by electronic scale. Waist circumference was measured to the nearest 0.1 cm starting on the right side of the body at the iliac crest. Measurements for regional bone, fat, and lean-tissue content were collected by whole body DXA scans. We estimated SMM using measurements of total lean muscle mass. Lean mass was estimated from DXA measurements in kilograms. Subjects with an SMM less than one standard deviation below the mean of a young reference group, which included males and females ages 20–39 from NHANES 1999–2003, were classified as sarcopenic. The cutoffs derived from the reference group were 48.37 kg for males and 34.57 kg for females. Waist circumference was used to define obesity given that it is less likely to be confounded with muscle mass than is body mass index (BMI). Furthermore, given that insulin resistance and inflammation are more closely associated with abdominal adiposity in comparison with other types of fat, we chose to use waist circumference given its ability to predict abdominal tissue mass located in the midsection. Obesity was defined as waist

circumference greater than 102 cm for males and 88 cm for females [19]. Because our obesity and sarcopenia measures may be confounded by height, we included a measure of standing height (in cm) as a control during analysis. Based on these cutoffs, four categorical groups were created—solely sarcopenic, solely obese, sarcopenic obese, and normal. Finally, although there is no cutoff for the lower end of waist circumference, 95.5% of subjects who would have been classified as underweight using BMI (<18.5) were captured in the sarcopenic nonobese group while the remaining 5% were in the reference group due to their healthy levels of muscle mass.

2.4. Insulin Resistance and Inflammation. Insulin resistance was determined through the use of the homeostasis model assessment (IR_{HOMA}) [20]. IR_{HOMA} is relevant to epidemiological studies and facilitates the estimation of insulin resistance using plasma glucose and insulin. It has also been shown to closely correlate with the insulin sensitivity index [21]. IR_{HOMA} was calculated as the product of fasting glucose (mmol/L) and fasting insulin (μ U/mL) divided by 22.5 [22]. CRP is a nonspecific indicator of general levels of systemic inflammation. In NHANES 1999–2002, high-sensitivity CRP assays were performed on blood samples using a Behring Nephelometer for quantitative CRP determination [18].

2.5. Potential Confounders. Age, sex, race/ethnicity, education, low physical activity level, and history of cardiovascular disease (CVD) were collected via self-report during the interview. In analysis, these were used as control variables as they have been found to relate to obesity, sarcopenia, and cognitive decline [23–29]. In the NHANES data, age was measured as a continuous variable, in years, and top-coded at 85 in order to guarantee anonymity among the oldest-old sample. Because cognitive functioning, adiposity, muscle mass, systemic inflammation, and insulin sensitivity are strongly linked to aging, our analysis is performed separately for the younger part of the sample, those aged 60–69, and those aged 70 and over. In our analysis for the younger group, a continuous measure of age was used as a control; however, due to top coding in NHANES, four age groups—70–74 years, 75–79 years, 80–84 years, and ages 85+ years—were used in the 70 and over group. Four categories for race/ethnicity were constructed using dummy variables to classify participants as non-Hispanic whites, non-Hispanic blacks, Hispanic, or other, with non-Hispanic whites used as a reference category. Education was assessed as years of school completed. Low physical activity level was assessed by asking subjects to rate their average physical activity level each day. Those who reported that they sit and do not walk around very much were coded as 1, while all others were coded as 0. CVD was coded as 1 in subjects reporting ever being diagnosed with one of the following: coronary heart disease, congestive heart failure, myocardial infarction, or stroke; all others were coded as 0.

Two indicators for poor nutritional status and dietary deficiencies, hyperhomocysteinemia and hypoalbuminemia, were also used as controls. These indicators have been found to vary by age and relate closely to both body composition

and cognitive performance. Homocysteine is an amino acid that at elevated levels may signal nutritional deficiencies. Total plasma homocysteine was measured using a fluorescence polarization immunoassay (FPIA) from Abbott Diagnostics, “Abbott Homocysteine (HCY) assay.” A cutoff of 15μ mol/L [30] was used to classify hyperhomocysteinemia. Serum Albumin, a commonly utilized marker of nutritional status [31], was measured using Boehringer Mannheim Diagnostics. The Bromocresol purple binds selectively with albumin, at the reaction pH [17]. Hypoalbuminemia was defined as serum albumin measures less than <3.8 g/dL. Although the typical cutoff for hypoalbuminemia is reported as 3.5 g/dL [32], it has been suggested that among outpatients this threshold may be too selective and could potentially miss substantially at risk older adults [33]. Thus, a more modest hypoalbuminemia level has been suggested for use in population studies [34].

2.6. Statistical Analysis. SAS statistical software package version 9.2 was used for all analyses. All analyses were run accounting for the complex sampling procedures in NHANES [20]. CRP and IR_{HOMA} were log-transformed to give them a more normal distribution and to better satisfy the assumptions of linear regression. Mean comparisons for cognitive functioning, log-transformed IR_{HOMA} , and log-transformed CRP were examined by age category and body composition, using a Bonferroni adjustment. A series of three ordinary least squares regression models were run for each age group to determine whether insulin resistance and/or inflammation impacted the association between body composition and cognitive functioning. The first model was used to determine the association between body composition and cognitive functioning, adjusting for demographic, health, and nutrition variables, including age, race/ethnicity, sex, education, height, history of CVD, physical activity, hypoalbuminemia, and hyperhomocysteinemia. In models two and three, log-transformed IR_{HOMA} and log-transformed CRP were added to the original model respectively.

3. Results

Demographic, physical, and examination characteristics of the sample are listed by age group in Table 1. Approximately, 49.01% of subjects were 60–69 years of age with a median age of 64, while 50.99% were 70 years of age and older with a median age of 76. Participants were 53.63% and 60.23% female in the younger and older age groups, respectively. Both groups were predominately non-Hispanic white, 78.33% in the younger age group and 83.16% in the older age group. The median education for both groups was 12 years. In the younger group, 23.51% had low daily physical activity, 15.25% had CVD, 3.83 had hypoalbuminemia, and 4.71% had hyperhomocysteinemia. In the older age group, these percentages increased to 30.76% with low daily physical activity, 24.70% with CVD, 5.11% with hypoalbuminemia, and 11.20% with hyperhomocysteinemia.

Distributions of body composition, by age, are shown in Figure 1. In the 60–69-year age group, 4.40% of the subjects met criteria for sarcopenic obesity, 59.17% were solely

TABLE 1: Sample characteristics for subjects by age group.

	Ages 60–69	Ages 70+
Age (years), median	64	76
Sex (female), (%)	53.63	60.23
Race/ethnicity, (%)		
Non-Hispanic white	78.33	83.16
Non-Hispanic black	8.97	6.08
Hispanic	9.45	9.35
Other	3.24	1.41
Education (years), median	12.00	12.00
History of CVD	15.25	24.70
Low physical activity	23.51	30.76
Hypoalbuminemia	3.83	5.11
Hyperhomocysteinemia	4.71	11.20

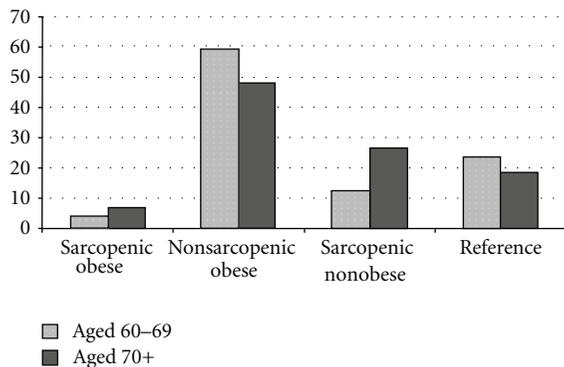


FIGURE 1: Distributions (%) of body composition by age.

obese, 12.63% were solely sarcopenic, and the remainder (23.80%) were neither obese nor sarcopenic. In the 70 years and over group, 7.04% of the subjects met criteria for sarcopenic obesity, 48.12% were solely obese, 26.53% were solely sarcopenic, and the remainder (18.30%) were neither obese nor sarcopenic.

Means for cognitive functioning scores and medians for IR_{HOMA} and CRP are provided by body composition and age in Table 2. For both age groups, nonsarcopenic obese subjects had significantly higher IR_{HOMA} , followed by sarcopenic obese subjects and, finally, sarcopenic nonobese subjects and nonsarcopenic nonobese subjects, who had statistically comparable levels of IR_{HOMA} . In both age groups, cognitive functioning scores and CRP differed significantly across all four body composition categories. Cognitive functioning was lowest among the sarcopenic obese group, followed by the sarcopenic nonobese group, nonsarcopenic obese group, and reference group. Sarcopenic obese subjects also had the highest levels of CRP, followed by subjects in the nonsarcopenic obese, sarcopenic nonobese, and the reference groups.

Table 3 examines the results from the three ordinary least squares regression models for the 60–69 age group. None of the unhealthy body composition groups were found to be significantly different from the healthy reference group in cognitive functioning score in any of the three models. Insulin resistance was not significantly related to cognitive functioning in this age group. On the other hand, CRP was found to be negatively associated with cognitive functioning. In model 1, 47.2% of the variance in cognitive functioning was explained by the variables in the equation. This is not increased in either of the subsequent models.

Table 4 shows the results from the three ordinary least squares regression models for the 70 and over age group. In the first model, all three sarcopenic and/or obese body composition groups were associated with poorer cognitive functioning. Relative to the healthy reference group, being sarcopenic obese was associated with an estimated 7-point decrease in cognitive functioning scores ($\beta = -7.08$, $P < .0001$), while being solely sarcopenic or solely obese was associated with estimated decreases of approximately 4.2 and 1.5 points, respectively ($\beta_{\text{sarcopenic nonobese}} = -4.19$, $P < .0001$; $\beta_{\text{nonsarcopenic obese}} = -1.43$, $P < .0001$). In model 2, insulin resistance was found to have a significant negative association with cognitive functioning ($\beta = -3.02$, $P < .0001$). The inclusion of log-transformed IR_{HOMA} in the model reduced the power of sarcopenic obesity to predict cognitive functioning by over 20% ($\beta = -5.66$, $P < .0001$). Controlling for insulin resistance also eliminated the association between cognitive functioning and nonsarcopenic obesity ($\beta = -0.51$, $P = .489$). In model 3, CRP was not found to be a significant predictor of cognitive functioning. Furthermore, with the inclusion of CRP, the power of sarcopenic obesity, sarcopenic nonobesity, or nonsarcopenic obesity to predict cognitive functioning was not significantly altered.

4. Discussion

Our findings suggest that body composition did not predict cognitive functioning in adults ages 60–69; however, for adults aged 70 and over, sarcopenia and obesity, either independently or concurrently, are associated with lower cognitive functioning when compared to nonsarcopenic nonobese older adults. Furthermore, we found that insulin resistance may account for a significant proportion of the relationship between cognitive performance and obesity, with or without sarcopenia. These results are consistent with findings that obesity, poor muscle quality, and insulin resistance [1–4, 15, 35] are associated with decreased cognitive functioning.

Age-related physiological maladaptations, such as metabolic deregulation, which are associated with abdominal fat, may simultaneously contribute to lower cognition and muscle mass, reflecting a degradation of multiple physiological systems. Insulin resistance, which often occurs as a result of the presence of excess visceral adiposity which increases with age, has been shown to alter lipid metabolism, increase systemic inflammation, disrupt endothelial functioning, and impact prothrombotic status and atherosclerosis [36]. As a result, many age-related diseases have been attributed to the steady increase in insulin resistance over the lifespan

TABLE 2: Insulin resistance, CRP, and cognitive functioning comparisons by body composition and age group.

Measure	Sarcopenic obese	Nonsarcopenic obese	Sarcopenic nonobese	Reference group
Aged 60–69				
IR _{HOMA} , median	2.72	3.68	1.92	1.89
CRP (mg/L), median	6.40	3.40	1.90	1.40
Cognitive functioning, mean (SD)	49.59 (23.1)	53.61 (18.2)	50.37 (20.3)	54.80 (18.4)
Aged 70+				
IR _{HOMA} , median	2.86	3.19	1.89	1.70
CRP (mg/L), median	4.20	3.00	2.60	2.30
Cognitive functioning, mean (SD)	32.92 (15.8)	43.66 (17.7)	38.26 (15.2)	45.88 (15.4)

TABLE 3: Coefficients predicting cognitive functioning for subjects aged 60–69.

	Model 1	Model 2	Model 3
Sarcopenic obese	-0.91 (1.30)	-0.83 (1.30)	-0.07 (1.31)
Solely sarcopenic	1.14 (0.93)	1.06 (0.93)	1.33 (0.93)
Solely obese	0.19 (0.62)	0.44 (0.68)	0.77 (0.64)
Black	-15.71 (0.93)***	-15.71 (0.93)***	-15.52 (0.93)***
Hispanic	-12.03 (0.98)***	-11.98 (0.98)***	-12.19 (0.97)***
Other	-7.52 (1.47)***	-7.39 (1.47)***	-8.61 (1.49)***
Age	-1.08 (0.09)***	-1.07 (0.09)***	-1.06 (0.09)***
Education	2.80 (0.09)***	2.80 (0.09)***	2.74 (0.10)***
Female	9.25 (0.78)***	9.12 (0.79)***	9.48 (0.78)***
Height	0.15 (0.04)***	0.15 (0.04)***	0.15 (0.04)**
History of CVD	-2.24 (0.72)**	-2.21 (0.72)**	-1.96 (0.72)**
Low physical activity	-3.12 (0.62)***	-3.06 (0.62)***	-3.11 (0.62)***
Hypoalbuminemia	-5.85 (1.29)***	-5.58 (1.32)***	-5.30 (1.29)***
Hyperhomocysteinemia	-4.98 (1.15)***	-4.99 (1.15)***	-4.97 (1.15)***
IR _{HOMA}		-0.37 (0.39)	
CRP			-1.01 (0.24)***
R squared	.472	.472	0.475

*P < .05 **P < .01 ***P < .001.

TABLE 4: Coefficients predicting cognitive functioning for subjects aged 70+.

	Model 1	Model 2	Model 3
Sarcopenic obese	-7.08 (1.28)***	-5.66 (1.28)***	-7.19 (1.28)***
Solely sarcopenic	-4.19 (0.82)***	-4.39 (0.82)***	-4.20 (0.82)***
Solely obese	-1.43 (0.68)*	0.51 (0.73)	-1.63 (0.69)*
Black	-14.33 (1.19)***	-14.23 (1.18)***	-14.40 (1.19)***
Hispanic	-9.19 (1.01)***	-9.56 (1.01)***	-9.33 (1.01)***
Other	-7.35 (2.03)***	-7.40 (2.01)***	-7.47 (2.03)***
Age (75–79)	-3.10 (0.59)***	-2.91 (0.59)***	-3.04 (0.59)***
Age (80–84)	-8.42 (0.68)***	-8.07 (0.67)***	-8.35 (0.68)***
Age (85+)	-12.02 (0.91)***	-12.49 (0.91)***	-12.03 (0.91)***
Education	2.25 (0.08)***	2.21 (0.08)***	2.24 (0.08)***
Female	3.68 (0.75)***	3.04 (0.75)***	3.80 (0.75)***
Height	-0.11 (0.04)**	-0.13 (0.04)**	-0.10 (0.04)*
History of CVD	-2.63 (0.61)***	-2.42 (0.61)***	-2.64 (0.61)***
Low physical activity	-3.11 (0.57)***	-2.83 (0.56)***	-3.14 (0.57)***
Hypoalbuminemia	-4.12 (1.44)**	-4.35 (1.43)**	-4.70 (1.45)**
Hyperhomocysteinemia	-0.11 (0.89)	-0.27 (0.89)	-0.26 (0.90)
IR _{HOMA}		-3.02 (0.45)***	
CRP			0.47 (0.24)
R squared	.387	.397	0.388

*P < .05 **P < .01 ***P < .001.

[36]. The association between insulin resistance and poor cognitive functioning may involve insulin-degrading enzyme (IDE), which plays a role in both insulin and β -amyloid metabolism. The accumulation of β -amyloid in the brain is considered one of the earliest detectable signs in the progression of Alzheimer's disease and is associated with cognitive decline, neurodegeneration, and synaptic dysfunction [37]. In the presence of insulin resistance, excess circulating insulin may prompt an increase in β -amyloid due to their competing demands for IDE [38].

Similarly, muscle weakness and deterioration, loss of lower extremity mobility, and changes in body composition, can also be linked to alterations in insulin sensitivity [39, 40]. It has been suggested that muscle metabolism may play a role in the development of sarcopenia, given that impaired insulin sensitivity has been shown to disrupt the anabolic effects on muscle proteins necessary for skeletal muscle conservation [40, 41]. As a result obese individuals with high levels of insulin resistance may be at increased risk of sarcopenia. On the other hand, the confluence of sarcopenia with obesity may have an even greater effect on insulin sensitivity, given that reduced muscle mass decreases the availability of insulin-responsive target tissue [42].

There are limitations in the present study which should be noted. First, the use of cross-sectional data hindered our ability to test for mediating factors or the temporality of our associations. Without a longitudinal design, we are unable to test whether insulin resistance precedes frailty and cognitive decline or examine whether subjects transition between body composition categories as they age. Second, our cognitive functioning variable was based on a single measure which did not take into account multiple aspects of cognition. Third, the use of imputed data on measures for muscle mass could be considered a limitation even though this is the procedure recommended by NCHS. Fourth, inflammation and insulin resistance are measured at only one point in time and may vary over time. Despite these limitations, the present study is strengthened by the use of reliable techniques for measuring body composition, the use of biomarkers to measure insulin resistance and inflammation, inclusion of a large representative random sample, and the use of appropriate sample weights and procedures during analysis.

The current study provides preliminary evidence to support the hypothesis that insulin resistance is an important mediator to consider in the association between sarcopenia, obesity, and cognitive functioning. With the doubling of obesity prevalence over the last two to three decades, industrialized countries are expected to experience a rise in the incidence of sarcopenic obesity among the elderly. Furthermore, given that both body composition and cognitive functioning have important implications for quality of life, healthcare costs, morbidity, and mortality, it is important to identify the underlying biological mechanisms which may predispose individuals to comorbidities, such as poor cognitive functioning, adverse body composition, and insulin resistance. In moving forward, the use of longitudinal data and the development of appropriate and reliable definitions for these conditions should facilitate our ability to understand the pathophysiology of age-related comorbidities.

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Review Article

Nicotinamide, NAD(P)(H), and Methyl-Group Homeostasis Evolved and Became a Determinant of Ageing Diseases: Hypotheses and Lessons from Pellagra

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Compartmentalized redox faults are common to ageing diseases. Dietary constituents are catabolized to NAD(H) donating electrons producing proton-based bioenergy in coevolved, cross-species and cross-organ networks. Nicotinamide and NAD deficiency from poor diet or high expenditure causes pellagra, an ageing and dementing disorder with lost robustness to infection and stress. Nicotinamide and stress induce Nicotinamide-N-methyltransferase (NNMT) improving choline retention but consume methyl groups. High NNMT activity is linked to Parkinson's, cancers, and diseases of affluence. Optimising nicotinamide and choline/methyl group availability is important for brain development and increased during our evolution raising metabolic and methylome ceilings through dietary/metabolic symbiotic means but strict energy constraints remain and life-history tradeoffs are the rule. An optimal energy, NAD and methyl group supply, avoiding hypo and hyper-vitaminoses nicotinamide and choline, is important to healthy ageing and avoids utilising double-edged symbionts or uncontrolled autophagy or reversions to fermentation reactions in inflammatory and cancerous tissue that all redistribute NAD(P)(H), but incur high allostatic costs.

1. Introduction

“Progress engenders Leisure whereby Energy is directed toward advancement of the Mind in all parts of Society that in turn receives new Energy.” Turgot, 1750.

“In my theory there is no absolute tendency to Progress, except from favourable Circumstances” Darwin, 1838.

Mental and neurological disorders are poorly explained yet constitute a good proportion of the global burden of disease, now defined as the inability to adapt homeostatically in the face of social, physical, and emotional challenges [1–3]. Robust brain development in the first place must help and is defined by environmental factors and cell types that evolve in a series of networks to ensure the efficient flow of energy and information [4–6]. Energy supplies

from food are a prerequisite for producing the necessary variety of cells and simultaneously act as a major selection force influencing their survival; yet despite its importance to brain evolution and development inequalities of diet, particularly over meat and calorific intake, remain a global issue, as do stress responses such as overeating [7–11]. Bidirectional circuits, from the energy supply to terminal fields, are selected from early exuberant developmental (but evolutionarily constrained) fields by environmental exposures but must have weak links as strong safety factors against every eventuality whether environmental, genetic or stochastic would be too expensive in energy terms. At risk circuits may include cholinergic, serotonergic, and dopaminergic systems that have not scaled up as fast as the overall three-fold expansion of the brain in the human primate [12–20].

Redox energetic faults and aberrant mitochondrial dynamics with consequent oxidative stress, and loss of

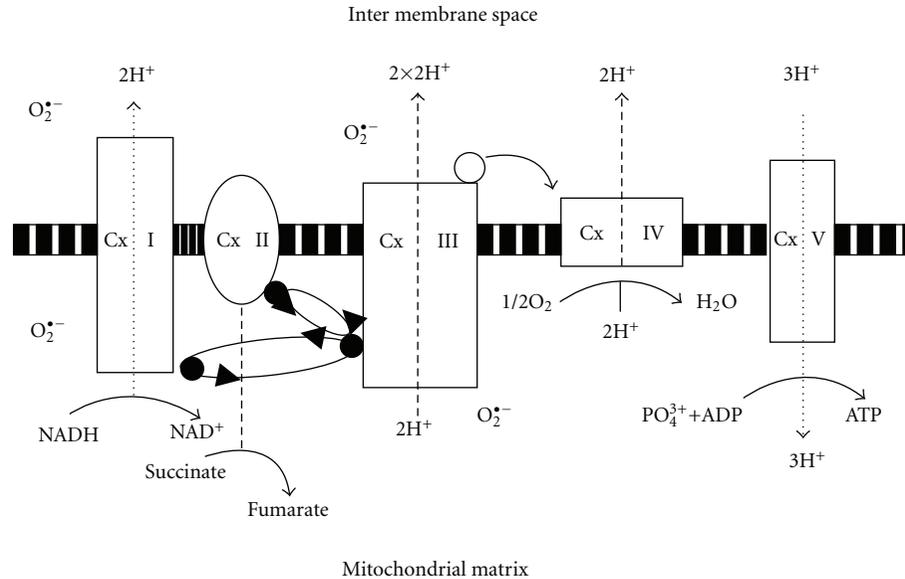


FIGURE 1: NAD(H)—the electron donor to complex I translocating protons across the membrane by a “steam engine” like mechanism producing ATP: the most important function of mitochondria alongside proton leaks for heat and energy dissipation and signals for autophagy and apoptosis. Many mutations that affect mitochondrial complex 1, or, microtubular function and kinases and autophagy/mitophagy and radical production contribute to rare forms of ageing diseases such as PD in a vicious cycle subverting normal quality controls that affect proteosomal homeostasis. In the case of Parkinsons’, increasing NADH levels may drive excessive dopamine synthesis to toxic levels by enhancing the recycling of the cofactor for tyrosine hydroxylase.

calcium, glutamate, proteasome, and inflammasome homeostasis are important proximate mechanisms of acute and chronic diseases and the physiological declines that are linked to ageing [21–31]. Some of these disease circuits may have particularly high energy requirements, for instance, those affecting higher intellectual and complex physical exploratory or reward functions using cholinergic or dopaminergic neurons: these for instance have mechanisms of autonomous pace-making with a high metabolic energy cost in terms of ATP to maintain tight control of intracellular calcium and complex redox needs involving cofactors, metals, and melanin [21, 32]. Confirmation of this fundamental and compartmentalized failure of the energy supply, often with impaired autophagy and mitophagy, comes from study of acute brain injury from hypoxia or hypoglycaemia or direct trauma, mitochondrial mutations linked with chronic diseases of ageing such as Alzheimer’s (AD), Parkinson’s (PD) and Huntington’s Disease, and, Complex 1 toxins (such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)) or rotenone and physical tests of endurance such as polar and high altitude expeditions [33–40]. The root cause of these diseases may be exposed energy and informatic links and responses with inadequate redox and mitochondrial potentials affecting proton based power and available ATP. Levels of cellular ATP affect all processes from muscle contraction to repolarization of neuronal membranes, to synthesis of cellular building blocks, to protection against microbes and toxins, and maintenance of proteins, RNA, DNA, and chromatin [41–44].

Now is an appropriate time to look at the effects of energy and the interlinked nicotinamide and methyl-group

under and oversupply and their relationships to information transfer and work outputs including those done to improve personal niche environments and evolutionary processes [45, 46]. This survey includes a historical episode when the nicotinamide, and tryptophan and hence NAD(P) supply (and potentially over 400 dependent reactions that influence every area of metabolism) failed as did the supply of methyl-groups. The forgotten case of the complex socioeconomic disease, Pellagra, may be a lesson about losing energy and redox “logic” at several hierarchical levels, and we intend to show that there may be current scope to adjust the dose of the macro- and micronutrients involved, across and within populations and according to individual need, aiming to improve robustness and resilience to a range of degenerative and proliferative diseases [47–49].

Background (1): Ageing Diseases, Evolution, and NADH. Current theories on ageing, lifetime behaviour patterns, reproductive cycles, intergenerational transfer of resource and stress responses invoke energy sources, sensors, regulators and tradeoffs: as do wider theories on the astonishingly rapid metabolic evolution of big brains aided by the ecological, social, and cultural strategies used by man that affect both access to energy useful information and increase in net energy input and allocation of energy resources [50–58]. Thermodynamically open and phylogenomic models support the idea that NADH and nicotinamide adenine dinucleotide phosphate (reduced) (NADPH) have had a central role and are the common currency in linking circadian environments to mitochondrial metabolism and vice versa [59–66] (Figure 1). Sharing hydrogen and its carrier around

Nicotinamide and NAD(H) interactions with cellular processes

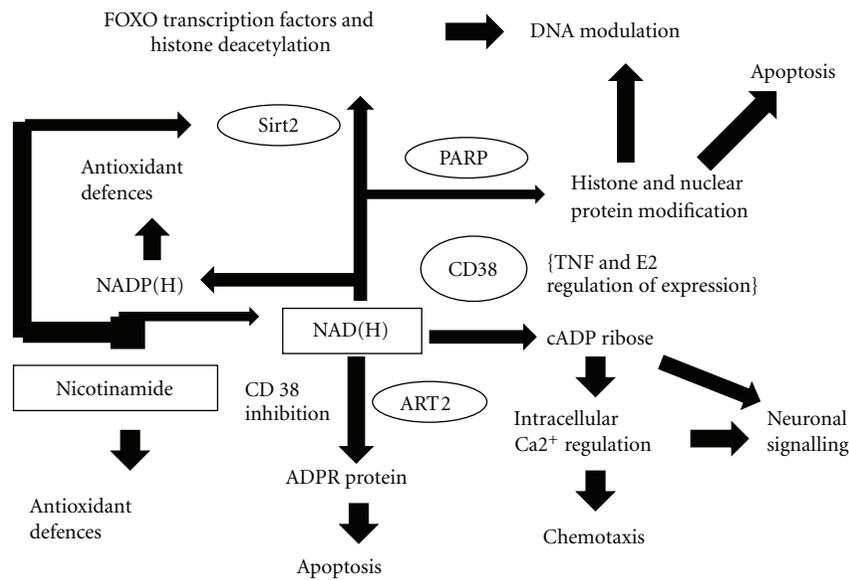


FIGURE 2: Direct redox regulation apart NAD-consuming pathways influences a prodigious number of pathways involved in internal metabolism and connections with the external world. Survival at the cellular level and of viable interactions with each other and diet and symbionts means that NAD and Nicotinamide are at the hub of the survival of superorganisms such as ourselves. Key: FoxO—forkhead transcription factors; Sirt2 and PARP in text; CD38 cluster differentiation 38; TNF—tumor necrosis factor; E2 Prostaglandin E2; cADP—cyclic adenosine di-phosphate; ART2—T-cell ADPRibosyltransferase; ADPR protein—adenosine di-phosphate ribose protein.

equitably as the source of electrons is complex relative to the supply of the electron acceptor oxygen that is free, but when successful enables efficient energy flows to be achieved: there is some danger from free radical damage from oxygen metabolism, though a prime importance of this for ageing is now in some dispute with the spotlight now on NAD and nicotinamide [67]. Efficient energy conservation in turn allowed the evolution of complex ecosystems and the expansion of genetic and species diversity, including the development of socially interacting brains working vertically down, up, and across generations often through NAD-dependent neuroendocrine and neurotransmitter mechanisms [68–76].

Recent reviews on nicotinamide and NAD metabolism, evolution and function concentrate on its pivotal role in gene silencing, development and ageing, through recently appreciated NAD consumers, such as the sirtuins (SIRT) [77–85], that evolved to work in large part as nutrient-sensing regulators, and poly (ADP ribose) polymerases (PARPs) [86, 87] and on the role of NAD(H) in Wallerian degeneration and neuronal death after a variety of insults [88, 89] (Figure 2). These reviews do not do justice to the importance of nutritional and symbiotic interfaces or the developmental dynamics of inducing NNMT, which partly regulates NAD(H) via controlling and detoxifying the supply of nicotinamide (vitamin B3), at the cost of losing S-adenosyl-methionine (SAM), the only metabolic methyl donor, or the related role of evolutionary history as the ultimate basis for understanding the proximate pathophysiology of a range of modern diseases [90–96].

Background (2): Symbiotic Energy Environments. Flow of energy largely determines the structure of ecosystems via food webs and taste sensors with appetite and quality controls, that avoid toxins but allows self-medication, and involve ATP sensitive autophagy in hypothalamic neurones [97–99]. Diet with concurrent domestication of microbes as gut symbionts (or yeasts to ferment foodstuffs) that break down proteins or indigestible starches or manufacture vitamins, including nicotinamide, has evolved to supply and translocate energy and information via circadian pulses of NAD(H): particular symbionts, for example, buffer particular diets such as those low in meat and dairy consumption or high in plant based carbohydrates [100, 101]. Disturbance of these symbiotic relationships, such as by the over-use of antibiotics, is receiving considerable attention in several conditions that are increasing in incidence currently [102]. Swopping production of vitamins and some catabolic enzymes from personal metabolism to diet or symbionts appears to help find hydrogen-based energy [103]. Diets (that both depend on and have shaped cultural niche constructions, such as farming selected crops, domestication of animals for milk and meat, and cooking) and the entangled symbionts which form the microbiome in the gut are essential synergies for the evolution of human life and energy harvesting directly through NADH/ATP production [104, 105]. Diet and symbionts compensate for each other by acting as coupled recycling systems at many metabolic, immunologic, and behavioural levels, and both are implicated when energy balances go wrong as in the case

of obesity, and when both are insufficient, gut cells may even break down their own components to obtain energy [106–111].

Failure of the supply of NAD(H) as a consequence of malnutrition or starvation triggers other attempts to compensate by autocannivory to avoid apoptosis or necrotic cell death, particularly important for neurones and other cells that are rarely renewed after birth [112, 113]. Immune/inflammasome modulation with such malnutrition also occurs and allows the organism to tolerate microorganisms which are potentially deleterious but are also capable of supplying NAD(H) or its precursors [114]. Reversion to fermentation occurs in inflamed or cancerous tissue, favouring net NADH export (the Warburg phenomenon) and interacts with autophagic mechanisms with recruitment of somatic oncogene mutations and methyl-group sensitive epimutations to achieve this metabolic milieu [115–119]. All the above may be homeostatic short-term attempts to correct a poor local energy/redox environment whether by producing, redistributing, or wasting energy to heat. As another redistributive example, ectopic fat stores, which include uncoupling proton-wasting inflammatory sites with loss of mitochondrial potential, are part of the metabolic syndrome to which populations that have recently undergone a nutrition transition are especially prone [120–123].

2. Pellagra

An NAD(H) deficiency state that illustrates the complexity of these coevolved energy networks was observed during the largely forgotten epidemics of pellagra caused by economically determined suboptimal foraging of nicotinamide and tryptophan (tryptophan is converted to NAD and serotonin) and dietary sources of methyl-groups. Such a dietary deficiency may still be important in sections of modern populations and intracellular and microenvironmental deficiency states can also occur from high NAD expenditure with NAD(H) ratios also affected by any disorder that causes hypoxia or hypoglycemia [124, 125].

2.1. Clinical Features of Pellagra. Scientific detectives investigating ageing diseases and human evolution should revisit a fork in the intellectual road that happened exactly a century ago for real-life ecological rather than solely laboratory-based clues around the NADH-NAD consumer axis (that are often controversial due to confounding factors in experimental design that try too hard to separate physiological homeostasis and stress responses from ageing or are too gene-centric given that most genes in some ecological context or other have survival value) [126–141]. Then the last major epidemic in man occurred (pellagra also occurs in several other carnivorous species such as dogs) with a systems failure of NAD(H) and therefore thermodynamic, NAD-Hub, and methylome homeostasis at all hierarchical levels. The epidemic started and ended socioculturally. Hypovitaminosis B3 caused a premature ageing condition with loss of robustness to chemical, physical, and emotional stress, leading to parkinsonism, dementia, metabolic disease, and cancer. It was conquered by dietary supplementation.

Famously, pellagra caused dementia, a characteristic photosensitive dermatitis (Casal's necklace), diarrhea, and death. The cause was real world economics creating NAD(H) gradients across poor populations, and across sexes (as it was twice as common in women) in the cotton- and corn-dependent states of the southeastern USA that reached epidemic proportions. Too much corn and molasses and too little meat led to a diet deficient in nicotinamide and probably other vitamins such as riboflavin and choline but often adequate or even high in calories. Currently a similar situation exists in parts of Africa. In the USA, familial aggregations were common, suggesting genetic predisposing factors and widespread epigenetic reprogramming. A diet with too much corn and too little meat caused deficiencies of nicotinamide and the essential amino acid tryptophan, though deficiencies in other vitamins, such as choline, and other methyl donors contributed to the malaise. Mental symptoms were wider than dementia, in that depression, fatigue, psychomotor retardation, mania, obsessions, and a whole range of psychoses with auditory and visual hallucinations were well described, along with personality change and sociopathic and drug and alcohol addictive behaviours. Panic disorders were seen as was a general inability to deal with physical or mental stress. Poor brain development such as hydrocephalus or cerebral palsy was also common. Acute delirium or even coma occurred, with some patients having myoclonus and other extrapyramidal signs reminiscent of the spongiform encephalopathies. The dementias of pellagra included features akin to Lewy body, Alzheimer's, frontotemporal, vascular, and prion diseases. Parkinsonism was also common and a festinant gait was first described in pellagrins. Tremors of various descriptions, including asymmetric rest tremors, were noted and some patients had typical paralysis agitans. Pellagrins had a characteristic expressionless faces, so some signs of parkinsonism were present in most cases. Many features of pellagra closely resemble the nonmotor aspects of PD.

The neurological manifestation did not stop there because other degenerative conditions, such as an amyotrophic lateral sclerosis-like picture, were described, with fasciculation of the tongue and upper and lower motor neuron signs. Cerebellar syndromes occurred and vertigo was frequent. Headaches, sensory and pain syndromes, epilepsy, and involuntary movements were noted as well as sleep disturbances. Cord lesions were also seen, as was optic atrophy, so there were multiple sclerosis (MS), like variants.

Non-neurological effects included the diagnostic photosensitive and ageing dermatitis along with diarrhea from multiple gut infections. Other infections including tuberculosis (TB) were common, suggesting a widespread effect on the immune system. There were also profound metabolic effects on the endocrine and thermoregulatory systems. For instance, endocrine dysfunction in thyroid and cortisol and reproductive pathways were all clearly described. Cancer rates were increased but masked by a high premature death rate.

Pellagra without dermatitis was well accepted and a frequently overlooked diagnosis. Young men from affected states had inordinate difficulty in passing the intellectual

tests that involved reading, writing and numeracy skills and the physical fitness tests required by the military, suggesting that subclinical disease was rife. Indeed poor diet and health have been implicated in the Southern states both having a tradition of violence (particularly toward the stealing of nicotinamide-rich livestock) and losing the American Civil War [142].

The classic pathological sign was chromatolysis of the high energy requiring pyramidal cells in the cortical gray matter but Purkinje cells also degenerated and there was a widespread cell loss in basal and sympathetic ganglia. Demyelination was commonly seen in the spinal cord, particularly in the posterior and lateral columns. Much was made of pigmentary change, glial overgrowth, vascular change, amyloid deposition, cytoskeletal and mitochondrial abnormalities and signs of inflammation and atrophy in all organs. A systems failure with the degenerative pathology of precocious senility was proposed by several pathologists in the late 19th century, and clinicians commented on patients as “wrecks of humanity”.

Pellagra is a wide systems failure in that an ecologic dietary stress triggers developmental and degenerative effects affecting behaviour and a vicious cycle which amplified the original economic stress. In addition, healthy members of society were phobic about pellagrins and showed them little if any empathy (unlike most other disabilities) and preferred explanations, such as a poor gene pool or that they were infectious, rather than blaming poverty. This picture, we suggest, may represent some aspects of human evolution gone wrong given that not only individuals but also their social relationships were all “wrecked”.

2.2. *Is Subclinical Pellagra Relevant to Contemporary Disease?*

Many poor individuals and groups, even in rich communities, have low amounts of vitamins in their diet. This assumes that the recommended daily allowance (RDA) for vitamins is correct for good health, as opposed to simply avoiding deficiency states. Consequently, subpellagrous nicotinamide deficiency may have lifetime roles in a range of behavioural traits, neuropsychiatric diseases, and dementias. Dietary choline deficiency exacerbates nicotinamide deficiency because metabolism of the two agents is linked; N-methylnicotinamide blocks choline export [143, 144]. Currently, trials of nicotinamide are underway in AD, stroke and several other neurological conditions based on the following [144–182].

- (1) The brain uses a lot of energy proportionate to its weight and glucose and oxygen status and NADH modulates memory retrieval.
- (2) In prospective studies, diets of AD patients were found to be deficient in nicotinamide pre-morbidly.
- (3) Nicotinamide reduces the accumulation of amyloid by an effect on secretases and affects the toxic effects of amyloid on astrocytes by inhibiting PARP and the NAD synthase nicotinamide mononucleotide

adenylyl transferase (NMNAT) that has protein-protein chaperone activity and also affects Tau-induced neurodegeneration by promoting clearance of hyperphosphorylated Tau oligomers.

- (4) In transgenic mice, nicotinamide restores cognitive deficits with effects on both dendrites and axons and reduces a phosphospecies of tau which is linked to microtubule depolymerisation, an effect also seen following the inhibition of SIRT1, and increases acetylated alpha-tubulin which is linked to microtubule and tau stability.
- (5) In models of AD, overexpression of SIRT1 or PARPs reduces memory loss and neurodegeneration.
- (6) Loss of SIRT1 is associated with the accumulation of amyloid-beta and hyperphosphorylated tau in the cortex of AD brains (thought to be compensatory changes to restore glucose/ketone metabolism).
- (7) Recovery of learning and memory has been associated with chromatin remodeling that happens with agents that affect SIRT and methyl metabolism and epigenetic mechanisms seem to be important in AD.
- (8) Energy paths involving cAMP and insulin-like growth factors are involved in memory consolidation and enhancement.
- (9) Dementia is being linked with both being under and over weight stress and exercise levels and the metabolic syndrome.
- (10) Nicotinamide reduces ischaemic and traumatic brain damage directly and via enhancement of the synthesis of NAD: both are common additional factors in many forms of dementia.
- (11) Redox active methylene blue affects dementia pathology and its clinical manifestations.
- (12) SIRT I regulates Notch signaling that is involved with mechanisms of action of mutations in the PSEN1 gene and the proliferation of neural progenitors in the subventricular zone important in the development and evolution of large cortical mantles and essential for cell specification and tissue patterning (and is involved in human cancer).
- (13) Nicotinamide and SIRTs are involved with promoting DNA repair particularly in oxidative stress circumstances.
- (14) Poor diet and chronic diarrhea affecting brain function may also interact with tradeoffs at genetic and antagonistic pleiotropic levels. Two copies of the e4 allele of apolipoprotein E lower the incidence of childhood diarrhea and poor cognitive development but increase the risk of AD later and appear to be within the reach of natural selection as do other genes affecting human longevity.
- (15) Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer mutations and PD-related mutations.

The neurology of HIV/AIDS, which includes premature ageing, dementia, and parkinsonism has clinical, pathological and biochemical similarities with pellagra [183]: many at-risk groups are nicotinamide deficient given that monophagic corn-based diets are now common in Africa. Both AIDS sufferers and pellagrins get many parasitic infections which may be dangerous homeostatic responses that boost NAD(H) in the host when dietary sources of energy are poor. Tuberculosis, for instance, excretes nicotinamide, is inhibited by nicotinamide and related compounds such as Isoniazid and treatment can precipitate pellagra and many gut infections/parasites break down otherwise indigestible cellulose, ultimately producing NAD(H) [184]. The HIV disease marker CD38 is a NADase that regulates intracellular NAD(H), implying disturbed nicotinamide-NAD(H) metabolism [185]. SIRT6 regulate the HIV transactivator Tat, promoting viral transcription and, through the NF-kappaB complex, induce T-cell activation particularly in dendritic cells and there are other links between NAD and the immune system [186, 187]. In view of the inhibitory effect of nicotinamide on SIRT activation and other actions, nicotinamide ought to be protective in AIDS and other chronic infections such as TB (that were particularly common in pellagrins) as an important missing host factor that affects virulence acting much like a vaccine [188]. Interaction between symbionts, such as the tuberculosis bacillus, happens by modulation of immune responses via tryptophan-NAD and mTOR pathways in dendritic and Th17 cells that have been under significant evolutionary pressures and span immune and energy pathways, even using ATP as a danger signal [189–193]. The tryptophan oxidation pathway is particularly interesting in the current context as it is both the *de novo* synthetic pathway for NAD (nicotinamide is like choline a semivitamin) and the tolerogenic pathway both for microbes and cancer and contains some potential neurotoxins and is disturbed in many degenerative diseases: enough NAD from vitamin B3 sources means less toleration of symbionts and at the extreme immune intolerance and allergic disorders [194, 195].

3. Hypervitaminosis B3 and Choline

Macronutrients and micronutrients, which include nicotinamide, choline, and other methyl sources, may all obey Bertrand's rule in that they have an inverted "U" shaped dose-response curve with toxicity at either extreme, as was suggested by Waaler regarding increased mortality at either extreme of weight/height ratio curves [196]. Affluent populations are exposed to diets with a historically high caloric content from refined sugars and fats relative to energy expenditure. In these populations, energy expenditure is relatively low because of limited exercise and the fact that body heat is maintained through living in artificial environments supported by the use of fossil fuels. Damage is often assumed to occur from the effects of an obesogenic environment rather than the more direct effect of disturbed NAD⁺:NADH ratios on a variety of dependent insulin, cortisol and other pathways (also affected by other bad habits such as smoking and alcohol and stress) with

obesity being an attempt to sequester energy and actively metabolise nicotinamide (more in keeping with its biological buffering role against starvation, even if it comes at a price) [197–199]. The relationship of the dose of the hydrogen source (caloric intake) with the dose of the suppliers of the carrier (NAD), derived ultimately from nicotinamide and tryptophan, that must be important for high quality biologically useful energy, has never been investigated in detail. Recently the possibility of both too little and too much choline in diet, modified by gut flora and genetic factors, has been raised in the context of vascular disease [200–202].

Extra choline and other methyl-group sources in diet from vegetables, meat, milk, and eggs during our evolution just like other key molecules such as nicotinamide would have enabled the development of cholinergic, glutaminergic, and monoaminergic systems that have actively evolved in primates and through, for instance, the NADH-dependent recycling of an essential cofactor, tetrahydrobiopterin, remain dependent on a good NADH supply for adequate learning and social and reward behaviour involved in sustenance and in desiring advance information, often mediated by dopamine [203–207]. Oxytocin/Vasopressin pathways are also important for the social interactions that have been so important to our evolution as are social substances such as alcohol which are also NAD-dependent, but all these systems may leave us prone to overindulgence as circumstances have improved [208–211].

4. An Evolutionary Perspective: Nutritional and Cognitive Transitions

An evolutionary perspective is warranted, because ageing of the cerebral cortex and basal ganglia is more prominent in humans than other primates, who also do not get AD or PD naturally (even though toxins such as MPTP produce a PD-like phenotype in the laboratory) and as living to old ages appears to have arrived late in our evolution and the ageing process may even finally stop [212–215]. High exposure to nicotinamide and choline and other dietary changes that boosted the overall supply of NAD(P)H may have been important ingredients of the change in diet of primates from a grass eating or herbivorous and fruit eating one toward one containing more starch from tubers and vegetables on to meat/marrow/brain eating. This triggered the 3-fold growth over 3 million years of the modern human brain and a high degree of control over the energy environment [19, 210–220].

This changed diet towards high quality energy (not just extra calories from "junk" food, because it combines high caloric content with key vitamins such as nicotinamide and several methyl donors (choline/folate/B12) and essential amino acids such as tryptophan and phenylalanine and lipid components such as Omega-3 fatty acids from fish [221, 222]). This change first happened in NAD(H) source rich patches of the less arid parts of Africa with repeated genetic and informatic bottle-necking as our species followed energy trails out of Africa and was facilitated by

the original invention of tools for butchery and later by hunting in groups and by the sharing and storing of meat [221]. Significant brain power is necessary for these group behaviours where individuals specialize and complement each other and read and anticipate minds of other hunters and prey and animal assistants with special sensory skills, and, learn to avoid toxic fauna and find natural medication now in a more seasonal and unpredictable environment. This brain power enables future-orientated thinking and delayed reward discounting, so that habitats or relationships were enhanced and not destroyed for short-term gain [223–227].

Preadaptations such as endothermy and earlier modifications of aerobic mitochondrial function enabling proton leaks and an ample blood flow to the brain to keep it cool for diurnal and persistent hunting may have helped [228]. Hominids, from *Homo Erectus* on, clearly went for acquiring multiple high energy sources. This enabled the resultant evolutionary advances via a positive feedback loop in which increasing energy sources that were easier to chew allowed the development of larger brains (but small teeth, masseters and guts), which in turn increased needs, which led to the search for more and greater energy sources as niche construction and included the use of exosomatic energy. However, our brain size may have peaked and it is smaller than the more carnivorous Neanderthals. In several species, domestication can lead to striking reductions in both cortical and striatal volumes surprisingly quickly, showing that this is a fluid process [229]. The invention of farming of grain and particularly meat and milk suppliers, followed by corresponding nutrigenomic innovations, that facilitated adaptations to new NADH-rich environmental opportunity, affecting lactose (milk is a valuable source of calories, pathogen-free fluid, and nicotinamide) and alcohol tolerance, amylase activity and nicotinamide methylation, happened on multiple occasions and spread fast [227–230]. This suggests very strong selection pressures working through both cultural and genetic inheritance, as does the rapid evolution and diversity of genes involved with mitochondrial function and glycolytic pathways [231]. This pressure seems to be every bit as important as mutational changes in genes directly affecting brain function [232–235].

Bipedal man is thought to have adapted fast, allowing time and energy to be freed up along with sedentism that in itself reduced energy expenditure from personal and child transport and by having a roof over their heads [236]. The resultant leisure led to the advancement of interactive minds and a distributed intelligence through multigenerational and multidirectional social structures with critical mass—important for divisions of labour—and a series of information revolutions that continue to this day (the “grandmother hypothesis” favours informatic and energy transfer but grandchildren may equally facilitate vertical transfers of certain resources such as new language or technological skills and have been an underrated factor in social cohesion and longevity).

Along with the social transmission of food preferences often mediated by acetylcholine release, which reduced the fear of novel foods, these information revolutions improved

decisions over the trading of and even inheritance patterns of energy sources and other materials [237, 238]. Intolerance of a restricted diet based on “fall-back” foods may also explain our love of flavour and the difficulty of finding single foods that are particularly protective against diseases rather than well-balanced omnivorous mixtures. The preference for a broad diet and the danger inherent in monophagy are evidenced by the many phenotypes seen with pellagra [239].

All in turn allowed advanced niche construction and the development of an energy-rich environment, which was enhanced by cooking that releases bioavailable nicotinamide unlike some other vitamins that are destroyed by cooking. Combined with other uses of fire, this enabled a more ecologically diverse and productive environment, such as increasing the number of available herbivores, so that less energy was expended on hunting but with greater certainty of success. Early man, through some degree of social independence and a consciousness, could move to brand new pastures or construct pastures new through planning, imagination, and innovation [240, 241].

5. More Recent History: The Neolithic and the Columbian Exchange

The history of maize, the crop that triggered pellagra, is a good example of coevolution because it is now dependent upon us for its sexual reproduction and we are very dependent on it as an energy source. The initial cultural spread of maize is one of the best examples of diffusion of innovation, which sometimes went wrong from lack of attention to detail. When it was imported to the southeastern states around 2000BC and later Europe from central Mexico as part of the “Columbian exchange”, it was improperly cooked and not combined with beans and squash or adequate meat. Maize is popular as it is a C4 plant with very efficient photosynthesis particularly when water is at a premium. New breeds underpin a large section of modern agribusiness. Together with other technoinnovations they have raised production from 1 Kg per hour on a Kenyan farm to 1000 Kg per hour on farms in Iowa [242].

Maintaining and enhancing the supply of high quality components, such as meat and milk, during the original agricultural revolution/Neolithic Demographic transition and over recent centuries has not always been easy and has caused tradeoffs between high population growth and health [243–246]. At times, micronutrient shortage such as lack of nicotinamide would have been more of a problem than shortage of calories and may be a mirror image of the much more recent contemporary demographic transition in Western industrialized societies. Population growth may have had a large part to play in the chronic malnutrition that has stunted growth and led populations to be prone to acute infection (which stresses the NADH axis); it has coincided with the coevolution of chronic infections (e.g., TB that excretes nicotinamide) and malaria (that affects NADH status, as do malaria resistance genes such as those causing G-6PD deficiency).

6. Affluence

A doubling of life span has occurred in many economies over the last 200 years, largely from the reduction in what were then common infectious diseases. Better diet has increased resistance to acute infections that compete for NAD resources as do their toxins. In the case of the so-called “infectious chronic unconquerables”, such as malaria and TB, there appears to be an immunological stand-off in which a degree of tolerance may have been traded for an increased supply of an essential nutrient. Many apparently healthy carriers, which were present in the dietary deficient population, literally disappeared as dietary standards improved in Europe and the USA. Thus, with the increasing quality of diet, symbionts become no longer necessary to supplement diet and the immune system can revert from controlling the population size of a mutualist parasite to trying to kill every invader. Recent information on the role of NAD modulating innate immunity suggests complex energy-centred interactions between neuronal and immunological systems. Contextually useful organisms (as seen in cases of pellagra) depend on ecological factors such as diet rather than geography or phylogenetic considerations, and on a good diet with changed prebiotic composition may no longer be advantageous. With the improved western diet, the immunological reaction to the formerly “useful” and actively welcomed biotic antigens concerned may be “confused” and may extend through molecular mimicry and nutrition-related signals to other antigens, thus setting off abnormal inflammatory and autoimmune reactions including to foods and pollens (that contain NAD(P)H oxidases). This is a different explanation to the more restricted hygiene hypothesis where lack of exposure rather than actively shunning “old friends” is postulated to cause immunological hyperreactivity [247–251].

Here we suggest the possibility that a hypervitaminosis B3 state, with both nicotinamide and N-methylnicotinamide having an optimal range, resulting from a western diet over-rich in meat and vitamin supplements working alongside calorific excesses may be implicated in other modern disease phenomena. Meat eating is preferred where it is available, though during pregnancy it is a common dietary aversion, suggesting that it can be toxic in early development as does the presence of the detoxification enzyme, NNMT and evidence of acute toxicity with nicotinamide overdose and worries about red meat being a risk factor for some cancers [252–254]. Nicotinamide exposure can be high, in excess of five times the recommended daily amount (15 mg/day) where diet has both cereals and “high energy” drinks supplemented with the vitamin and where there is an abundance of cheap meat and milk. This chronic overload can be envisioned as working through unbalancing NAD(H)-dependent systems, including SIRT1s and PARPs or dehydrogenase pathways (for instance in cortisol metabolism), and through the direct effects of nicotinamide or N-methylated metabolites. NAD⁺ is the substrate for SIRT1s and nicotinamide is an inhibitor, so dietary levels of NAD(H) precursors could act as both positive and negative influences on such systems. In the case of nicotinamide, dietary inputs are modulated in part

by genetic determination of NNMT levels, with 24% of the population being high expressors. Nongenetic factors also modulate expression of the enzyme. These include nicotinamide itself, stress and the demands imposed on NAD(H) availability by growth, tissue repair and exercise. Interestingly, NNMT and other components of NAD(H) pathways are markedly induced in a variety of currently common cancers as well as in the metabolic syndrome, obesity, PD and autism [255–262].

An animal model of toxicity from excess dietary nicotinamide has been reported. In this model, dopaminergic neurons were damaged and locomotor activity was reduced. In addition, this model responded to L-DOPA [263]. In other models, nicotinamide and novel derivatives such as N-Nicotinoyl dopamine can reduce melanin as happens in PD [264, 265].

One consequence of NNMT induction and other methyltransferase reactions is a depletion of methyl stores and S-adenosylmethionine (SAM) that is ultimately dependent on an adequate dietary supply from expensive vegetables and meat rather than cheaper cereals such as corn (banned in 19th century France as unfit for human consumption, thus eliminating pellagra at a stroke: a lesson for modern Africa) [266]. Depletion of available methyl groups, whether from a poor diet or one with excessive nicotinamide, may be a common cause of epigenetic phenomena given the marked influence methylation has on gene expression in pluripotent and differentiated cells that maintain cellular identity [265]. The methylome is an important mediator of information and modifies gene transcription and translation including riboswitches affecting RNA metabolism and in toxicology pathways in concert with NAD and ATP and all appears to be involved in a number of diseases seen within the pellagra phenotype such as cancer and motor neurone disease [267–272]. A major role for the methylome is well accepted for many cancers and their related epimutations sometimes working in concert with DNA sequence mutations in tumour suppressor and DNA repair genes and may well be modifiable by diet [273–277]. There may be several mechanisms whereby such metabolic programming can be inherited and affect offspring [278].

7. A Deep History of Hydrogen and Hydrogen Symbioses: Origin of Cooperative Species [279–281]

Life without hydrogen is impossible, whether free or bound with NAD(P) as energy or with oxygen as a solvent. The sun burns hydrogen in a fusion reaction and emits light energy. Early life chemo-litho-autotrophs used redox gradients including hydrogen as the electron donor and then the earliest animals developed symbiotic relationships with bacteria that produced hydrogen and the invention of photosynthesis split water to produce hydrogen as NADPH and oxygen (earlier forms split H₂S). Hydrogen can escape from the earth and led to the great oxidation events and an oxygen atmosphere that along with important symbiotic acquisitions involving chloroplasts, hydrogenosomes, and

mitochondria allowed the evolution of complex plants and the rise of an animal kingdom that eats hydrogen sources or has gut symbionts that produce hydrogen equivalents from otherwise indigestible foods. Too much hydrogen escape from splitting of water by radiation in the upper atmosphere creates “runaway greenhouse” effects that are incompatible with life and may have happened on other planets and could happen here. Early mammalian inventions that would increase hydrogen and nicotinamide sources include placental and milk feeding. Healthy energy ecosystems reduce poverty and underpin healthy interactive economies: and even though modern economies appear to move away from a primary reliance on natural capital and capturing solar energy, we all need to eat well to stay healthy and need to appreciate the real source of our prosperity and the need to avoid food crises worldwide.

8. Longevity and Nutritional Balance

The NAD(H) energy path and NAD consuming hubs are involved in many key cellular processes and in the regulation of food intake and the phenomenon of caloric restriction and hormesis (that which does not kill you, whether diet, toxin, emotional, acute infectious or traumatic stress, makes you stronger) which are implicated in many diseases of ageing [282–302]. These hubs are amenable to therapeutic intervention and may unwittingly have contributed by a better overall diet and energy budgets to recent increases in longevity in affluent countries (Figure 2). Age-related changes in NAD/NADH ratios have been noted and a world where NAD is central postulated [303, 304]. Placebo effects that are so prominent in man also have been linked to energy pathways and are particularly effective when the energy future is perceived as healthy, allowing energy to be invested in healing rather than fire fighting [305]. Endocannabinoids that depend upon the organisms energy status may translate food availability into fundamental choices about development which affect lifespan, and some addictions that were common in pellagrins such as Nicotine are also closely linked to energy pathways. Caloric restriction hints at the need for a nutritional stoichiometry to balance energy demand and supply throughout life. It is associated with telomeric stability and increased SIRT 1 activity stabilising PGC-1 and results in increased mitochondrial biogenesis, metabolic function, and the deacetylation and inactivation p53. This balance may be more about $\text{NAD}^+ : \text{NADH}$ ratios than calories per se, which may explain the perplexing and contradictory role of NAD-consumer agonists (such as resveratrol) and antagonists in disease models. SIRT1 knockouts show widespread p53 activation and shortened life expectancy [306]. Increased longevity as a result of caloric restriction and related genetic models fits with abundant evidence that nicotinamide is involved in neuroprotection [307–318]. The damaging effects of too low a dose are a matter of historical record. Evidence is emerging on excessive intake of the vitamin [319, 320]. Nicotinamide’s actions may be double-edged as although it is efficacious in a wide range of current insults and pathologies too much may be as harmful as too little.

Links between nicotinamide, acetyl and methyl metabolism and epigenetic phenomena are strong [319, 320]. Other recently studied famines such as the Dutch hunger winter of 1944–45 and the Chinese famine of 1958–61 had marked long-term and transgenerational effects on health such as the risk of the metabolic syndrome but also psychiatric and antisocial behaviours working through epigenetic mechanisms: those affected would have been NAD(H)-deficient with an element of pellagra [321, 322]. Optimising choline and other aspects of methyl metabolism in embryonic life improves brain development and strikingly reduces age-related declines, perhaps through reducing epigenetic instability. Epigenomes, which may be marked by dietary, emotional, and intellectual experiences working through neuroendocrine stress pathways that themselves are redox and energy-regulated and implicated with many “modern” diseases, can be assimilated into the germline and are unstable, creating somatic epimutations during mitoses, some of which may be resistant to erasure. Surviving epigenetic imprints may be the missing transgenerational elements, along with nonshared environments (merging nature and nurture), causing both familial clustering and sporadic cases in diseases such as AD and PD. Twin studies show low concordance in AD and PD, thereby demonstrating the importance of environmental dynamics and chance epigenetic drift over lifetimes [323].

9. Development to Decline: Managing Metabolic Expectations

Within the context of lifetime availability of NAD(H), where in adult life the net free energy or the availability of methyl groups is greater or lesser than that in early life or expected *a priori* by the genome of the individual, an imbalance between (epi)genetic-primed protein inductions and nicotinamide may occur if circumstance overcome tastes, habits, and addictions that attempt to stabilise intake. This imbalance is more nuanced than might be expected and not simply due to the fact that modern diets are mismatched with genetic “thrifty” gene hangovers from the Pleistocene [324]. Our evolutionary history of extreme fluctuations in meat intake from low to high as hunter-gatherers to patchy and still in transition is likely to be more relevant. Nutrigenomic and informatic adaptations and changes in tradeoffs resulting from knowing that the energy future is often more likely to be benign have occurred over the last 100,000 years and during individuals lifetimes. Low levels of nicotinamide and choline in early life adversely affect neonatal brain development and later degeneration [325]. Low NAD(H) levels in the foetal/neonatal period could result in a phenotype which could be reinforced by low levels through life, giving rise to poor brain development and function. High early levels could lead to good brain development (“luxury” phenotype) but a drop in the supply later in life, even to average levels when NNMT, the catabolic enzyme, has been induced, could trigger intracellular pellagra. If the NAD(H) and nicotinamide supply is superabundant throughout, life toxicity might result from excessive N-methyl-nicotinamide, a MPTP lookalike (Figure 3). This is plausible because

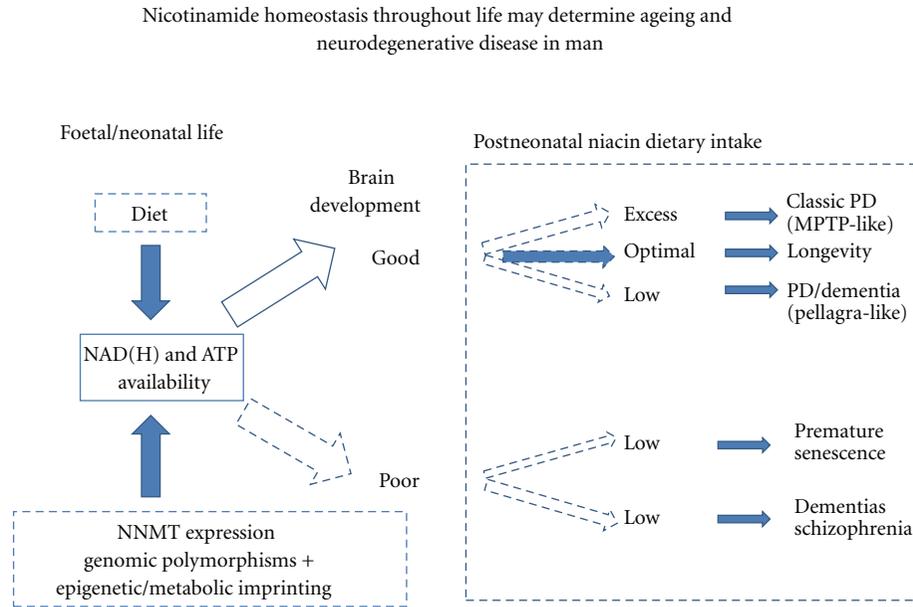


FIGURE 3: NAD(H) availability is key to good brain evolution and development. An inherent weak link is poor supply or a potential imbalance between induction of NNMT and nicotinamide and choline intake in early and later life with a risk of late degenerations such as Alzheimer's and Parkinson's disease. Overinduction of NNMT by nicotinamide could paradoxically cause intracellular pellagra perhaps explaining why nicotinamide can appear to help short-term even though nicotinamide may be a long-term toxin. In addition, poor diet or induction of NNMT disturbs the methylome and the epigenome creating cancer promoting epimutations.

nicotinamide and redox status have marked morphogenic effects that instruct internally secreted morphogens which regulate all phases of neuronal development and in effect brain evolution [326–328]. The effects can become pathological when unexpected energy circumstances are encountered, as seen with metabolic syndrome, and we propose neurological disease [329].

10. Metabolic Fields

Accumulating evidence points to the probability that ageing diseases such as AD, PD, cancers, and metabolic diseases originate in mitochondrial depolarisations and uncouplings with disturbed electron-proton flows as “protonopathies” and have consequent effects on ATP [330–333]. A unifying explanation imagines abnormally spreading metabolic fields, if the challenges of balancing NADH- dependent energy supply and demand and the need for optimal methyl group availability that arises during growth, reproduction, exercise, and tissue repair are not met; most cancers, for instance are demethylated and have changed their energy metabolism profile even in precancerous stages [334]. These challenges could happen at the same stage of life in diverse species, explaining similar incidences of cancer and degeneration despite large variations in numbers of cells/body size and longevity that are hard to explain on a somatic mutational or purely immunological basis which may be secondary or compounding phenomena [335]. Reactions to stabilize metabolism by excreting NAD(P)H (essentially a waste product not a source of energy in cells using anaerobic metabolism) or other reducing equivalents (e.g., lactate),

such as autocannivory/autophagy/apoptosis and the Warburg effect (such that both the oxic and, of course, the anoxic portions of the tumor are both fermenting) could spread like a wave: as do their pathological correlates, whether degenerations, infections, or cancers. NAD metabolizing ectoenzymes and salvage pathways appear to be important in shaping tumor-host interactions with mitochondrial pathways affecting whether or not cancer cells live or are primed for death [255, 336–344]. NNMT activity affects proliferation of cancer cells, affects radiation sensitivity, and alters free radical production; nicotinamide affects genomic instability and cancer cells eat tryptophan [340, 345, 346]. These heavily involved pathways have opened therapeutic possibilities for several tumours including glioblastoma where the importance of mitochondrial dynamics is increasingly recognised [347]. In cancer cells many germline and somatic mutations continue to evolve as cancer spreads, for example, in p53 and relevant receptors, such as those for steroids and growth factor signals. Thus glucose uptake and mitochondrial and isocitrate and phosphoglycerate dehydrogenases and pyruvate kinases are affected, allowing multiple switches from oxidative metabolism to net NAD(P)H production affecting both energetic and redox buffering/antioxidant capacity [262, 348–355]. The paradox here if solely seen from the cancers point of view, rather than viewing this as a pseudo-symbiosis, is that the growing tissue is wasting energy and the argument that it gets ATP faster through glycolysis is weak [356]. Cancers cannot always be eliminated and often recur (though occasionally spontaneously remit) or a second cancer develops, suggesting that the basic problem is not eliminated by simply killing cancer and surrounding normal

cells (which may however temporarily improve the local energy environment by releasing ATP and its precursors).

Foetal implants develop PD pathology, illustrating the point that the niche microenvironment is the key [357–363]. Stem cell implants in PD and other conditions survive and connect but form strange lesions and connections suggesting that lack of stem cells is not the real deficit. Rather stem-cell-based therapy from the haematological transplant to those for other organs involves the efflux of NAD and ATP into the extracellular space or autocrine induction of NAD release activating purinergic and calcium pathways affecting growth-supporting and antiapoptotic activities relevant to their therapeutic effects [364]. Parabiocotic fusions of young environments rejuvenate cells, even those expressing pro-cancerous somatic mutations or destined for autophagy [365] and changing the ageing milieu, alter neurogenesis and improves cognitive function. Stem cell fates toward both normal and abnormal differentiation or dedifferentiation depend on their microenvironment and stochastic factors, and even cells that are already cancerous can be induced to behave normally [366–369]. Protein folding and the function of amyloid/synuclein/prion proteins and ionic and neurotransmitter gradients are exquisitely sensitive to energy landscapes, as are NAD(H)-consumer linked DNA repairs. Consequently, all these phenomena, when abnormal, may be secondary and late effects of abnormal NAD(H) ratios and methylation status affecting epigenomic phenotypic plasticity.

11. Regeneration and Degeneration on Purpose

In complex organisms stem-cell-driven regeneration, which could compensate for long-term damage that is beyond repair, is suppressed particularly in the CNS, whilst dying cells from traumatic injury releasing NADH equivalents may be a potent stimulus for regeneration in other tissues and simpler organisms [370]. This apparent design failure, which is actively pursued by complex organisms, may be rooted in energy allocation models, that is, in tradeoffs that favour building spare capacity during development. Spare capacity when young, which can be coopted as an exaptation for early in life innovative thinking about the environment, may be evolutionarily more advantageous than maintaining, at high cost, regenerative machinery permanently on stand-by that may never get used.

The brain functions within the constraints of an energy (ATP) budget, with high levels of energy used to process information from the environment via action potentials and less energy intensive metabolic processes used to recycle neurotransmitters [371–374]. There is evidence that this budget evolved to permit other tradeoffs allowing neuronal energy costs to remain low while still allowing the organism to gather all required information. In environments where certain sensory information is not needed, evolution has led to the loss of superfluous sensory systems. This responsive and adaptable evolutionary process can also lead to the addition of sensory systems as required by changing environments. Such additions and deletions develop as a result

of an advantageous cost/benefit analysis by the evolving organism responding to changing environments and to learn for specific tasks as well as for general intelligence [375].

Poor development from poor early energy circumstances and loss of reserve capacity would be expected to cause late problems, as suspected with AD. Nevertheless, continual regeneration and selection of circuits that are using energy are constantly occurring by altering mitochondrial and SIRT function, and bioelectric free energy and proton fields and fluxes, that influence positional memory and regeneration of even complex structures such as the spinal cord (giving hope that improving the NAD(H) and methyl environment is never too late) [7, 376–378].

12. Energy Circuits Can Breakdown

We live in a complex habitat and an energy and informatic subsistence environment largely of our own making that has driven our brain and behaviour patterns to ecological rationality, in order to cope with being far from thermodynamic equilibrium, with strong positive feed-forward decision-making and negative feedback homeostatic mechanisms that drive progress. Less fortunately disease phenotypes from the cancerous to the neuropsychiatric happen when it goes wrong, as happened in the case of pellagra. Pellagra like most famines was not wholly caused by natural disasters but man-made collapses at a series of hierarchical levels from the social to the subcellular. Ever since *Homo Erectus*, our genus has been addicted to acquiring more and more energy, first as NADH and then harnessing all forms of energy, with a push from coping with poor energy environments and a pull from using excess energy to best advantage through the use of our collective imagination and each other: much current intellectual effort is currently expended on discovering new sources of energy especially those based on hydrogen [379, 380] (Table 1). Many memes/ideas are generated and their survival may often have been dependent upon whether they contain energy-useful ideas, with logic systems working at biological and behavioral levels building on simpler circuits such as the iconic transcriptional regulation of the lac operon in response to changing energy sources. This requires a high quality diet and gut symbionts forming superorganisms with extended metabolisms that are not simply divided by skin or skull from the world but are complementary systems that still have fault lines that can breakdown. Self, as usually defined by the immunologists, is misleading, and more modern views on metagenomes are closer to the mark and, like the psychologist William James, define self as “all a man can call his” and includes his sources of energy and information [381].

Despite consuming a high proportion of the body's energy, brains are efficient (Watson, IBM's latest AI answer machine runs on 100 Kw compared with 100 w for a brain) and lose functions no longer used, suggesting strict constraints on bioenergy allowing the brain to continually evolve along with the changing environment, with considerable potential for human enhancement if the environment improves [382]. Enrichment of the cell's microenvironmental energy ecosystem and a “use it or lose it” strategy

TABLE 1: Three worlds that interact are largely human thermodynamic and cognitive niche constructions that are all heritable making us codirectors of our own and our collaborators evolution. There is a cost to this cumulative evolution that may include hypo- and hypervitaminosis, energy, and informatic states.

Thermodynamic and material	Personal	Information and society
Omnivorous diet	Conscious perception	Divisions of labour
Trading symbionts	Empathy	Trading
Shelter/clothes	Mental time travel	Information stores
	Know-how	
	Language	
	Nutri-genomics	
	Immunogenomics	
	Neuro/endocrine homeostasis	

Surplus energy for innovation of tools and technology and further harnessing of energy.

leading to energy flow may be key to improvements in the longevity of many cell types and in prompting neural stem cells, “hungry for action”, to divide. Maintaining optimal NADH:NAD⁺ ratios and methylation status through dynamic energy budgets in every compartment is a continual challenge which is awe-inspiring in its complexity. Nevertheless, such considerations are necessary for every single cell if they are to avoid death or cancerous change and may be aided by quantum effects on the distribution of energy [383]. High energy circuits and electrical waves, such as gamma oscillations, are needed for intellectual hippocampal and motor programmes that require strong functional performance of mitochondria and particularly need the pyramidal neurones that take a big hit in pellagra [384, 385]. These circuits are synchronous with circadian NAD(H)-dependent informatic rhythms between individuals and their diets, symbionts and social relationships and beliefs, some mediated by hormones such as oxytocin and neurotransmitters such as dopamine. Sleep gives time for synaptic normalization after dealing with ever-changing environments and unsustainable consumption of energy with saturated abilities to learn as environmentally cued memory and free-will decision making, over and above reflex preactivation of volition, require particularly high energy levels: these are functions hit early in cortical and basal ganglia degenerations some of which compensate by the patients developing a sweet tooth or otherwise modify energy intake or expenditure as part of the symptoms or attempts at treatment [386–396].

These environmentally coupled systems, largely of our own making to keep energy flowing and balancing excitatory and inhibitory circuits, can get decoupled with energy or informatic under or overload (“rewired and running hot”) and may be hit preferentially in PD and AD and other diseases peculiar to Homo sapiens, such as depression and psychoses where nicotinamide aberrations have long been suspected [358, 359]. We urgently need to improve our abilities to measure or image suitable NADH supplies in a series of human habitats on the outsides of our Russian Doll Redox arrangement and NAD(P)H/NAD(P)⁺ ratios in every internal compartment, cell type and organelle as early warning systems to intervene and avoid pathology even getting started.

13. Conclusion

Classical pellagra is an archetypal energy and NAD supply-side premature ageing disease, with excessive use of symbionts and degenerative pathology, that has been cured but we have never checked to see whether subpellagrous NADH deficiency has been eliminated. Sub pellagrous NAD deficiency may be a man-made socioeconomic “place” disease that rears its head episodically as a “time” disease triggering age-related infections, degenerations, and cancers [397]. This type of socioeconomic illness does not naturally trigger an empathetic response reducing the chances of resolving the situation [398]. Interactions with other vitamins may be important either with deficits or excesses as we have implied for choline, and for example, the combination of low vitamin D intake with genetic predisposing defects, and, NAD supplies, and, altered relationships with microorganisms triggering autoimmune demyelination may be important in the pathogenesis of multiple sclerosis [399, 400]. Intracellular pellagra may also be caused by other mechanisms such as high NAD expenditure after physical, emotional, or chemical toxic stress or acute infection or inadvertent removal of key symbionts, such as after antibiotic use, or mutations that impair autophagosome functions such that at some times or for some people the dose may need to be higher than usually recommended. Stress from loss of relative status is a powerful driver of ill health and primates including man revert to a high glucose and low nicotinamide diet or addictive behaviours that as with stress also induce NNMT that will further lower nicotinamide levels [401, 402].

One should not, on the other hand, expose populations to “too much of a good thing” with excessive supplies of nicotinamide or choline or calories and thereby perturb NAD:NADH ratios in favour of NADH, creating a mirror image of pellagra, perhaps with an equally broad phenotype [403]. Modern disease patterns may be contemporary mirror images of the Neolithic meat transition when with less meat fertility rose but so did disease reducing longevity, whereas now as meat eating is on the increase longevity is increasing with fertility dropping and different chronic diseases emerging, and others such as TB rapidly decreasing.

Poor worldwide distribution of NAD(H) supplies makes little sense if oversupply is dangerous, particularly if under-supply is not only dangerous to those affected but leads to new symbionts or drug resistant microbes aided and abetted by the host in metabolic desperation that can then infect others who are more affluent and cause potentially epidemic pathology [403]. Our current behaviour that does not deal with this urgently “altruistically” may need the insight that as group sizes were enlarged we moved away from our hunter-gatherer roots of an egalitarian norm and a sharing of nicotinamide and methyl group rich meat. “Stinginess” may date from when the natural meat supply deteriorated and meat and the considerable wherewithal to produce it became treated as property. Fighting and migrating were preferred over starving, and trading may have promoted specialisation, competition, and inequality including of access to meat [404]. Resource allocation both of food and of medicines is culturally driven with a tension as to whether those that earn the most or those with the greatest need are given preference. The former is the usual modern default option but is a cultural “homo-economicus” evolutionary trap that needs to be consciously and socially corrected [405–407]. Fairer access to high quality energy sources allows all people the choice of moderation and a Hippocratic style diet and exercise regimen, and, access to parallel drug developments which have hormetic and preconditioning effects: that test the energy axis, induce autophagy and unfolded protein targeting and endoplasmic reticulum stress responses to recycle protein debris, thus preventing and “vaccinating” against disease [408–410]. New treatments that quickly supply energy, or save energy by inducing artificial hibernation, if employed after an unexpected insult such as trauma, and allow natural healing to take place, may also work best [411].

Humans have been exploring ways of preventing cancer and degeneration for decades whereas evolution has coped with episodes of NAD(H) deficiency and excess for several billion years. Now it may be time to learn lessons from the experts and find a Goldilocks energy-methylome-informatic-economy that matches supply and demand throughout life. Fewer energy tradeoffs or faulty signals may avoid lost robustness, shorter lives and loss of a fitness trait such as intellectual or physical capacity as seen with the degenerative AD and PD or the proliferative cancers, inflammatory and allergic diseases.

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