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Review Article

Cardiac Effects of Exercise Training in Hypertension

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Hypertension is a significant health concern. Hypertension leads to compensatory pathologic hypertrophy and impaired cardiac function. Lifestyle modifications such as exercise are encouraged for hypertensive patients. Some studies have shown that exercise training can reverse pathological hypertrophy. Conversely, studies on animal models of hypertension have shown increased cardiac growth with exercise training. Despite the further induction of hypertrophy, exercise training seems protective against cell death and may increase cardiomyocyte proliferation, leading to a putative phenotype. One of the hallmark beneficial effects of exercise in hypertension is an improvement in myocardial β adrenergic responsiveness. The focus of this paper is to discuss how exercise training impacts cardiac remodeling and function in the hypertensive heart with specific reference to β adrenergic signaling.

1. Hypertension and Blood Pressure with Exercise

Hypertension is a significant health concern, as it afflicts over 65 million individuals in the United States [1] and 1 billion people worldwide [2]. The residual lifetime risk for developing hypertension in middle and older ages is 90% [1, 3] and its prevalence has increased by 30% over the last decade [1]. Moreover, with the number of older individuals on the rise, the prevalence of hypertension is certain to increase. This is a significant issue in the epidemiology of cardiovascular disease, as hypertension increases the risk of ischemic heart disease, stroke, and heart failure [1]. A key initiative in offsetting the consequences of hypertension is preventing or attenuating its negative sequelae in the first place. In this regard, several expert joint panel reports support the idea of lifestyle modifications such as exercise/physical activity, diet, and smoking cessation in the initial management of hypertension [1].

The effects of chronic exercise training on blood pressure have been well studied. In normotensive subjects, there is an approximate 3-4 mmHg reduction in resting systolic and diastolic blood pressure following training [4–6]. In hypertensive subjects, the reduction in blood pressure is even greater, that is, 6-7 mmHg reduction after training [6–9]. Aerobic exercise training has also been shown to reduce blood pressure during exercise [7, 10] and ambulation [7, 11, 12]. Acute aerobic exercise has even been shown to cause a relative hypotension during the postexercise recovery phase [13]. Thus the overall reduction in blood pressure with aerobic exercise training attenuates afterload on the heart and is the hypothetical basis by which exercise may mitigate cardiac hypertrophy in hypertension.

2. Heart Remodeling with Hypertension

2.1. Compensatory Hypertrophy. Chronic hypertension negatively impacts both myocardial structure and function by serving as a substrate for the induction of pathological, concentric hypertrophy (Figure 1). It is thought that the hypertrophic cardiac response to increased pressure overload is an attempt to normalize left ventricular wall stress thus helping to maintain cardiac function in the face of an enhanced hemodynamic load. This process is referred to as "compensatory hypertrophy."

With compensated myocardial hypertrophy, the heart remodels by the parallel addition of sarcomeres that characteristically increases cardiomyocyte area and width [14, 15].

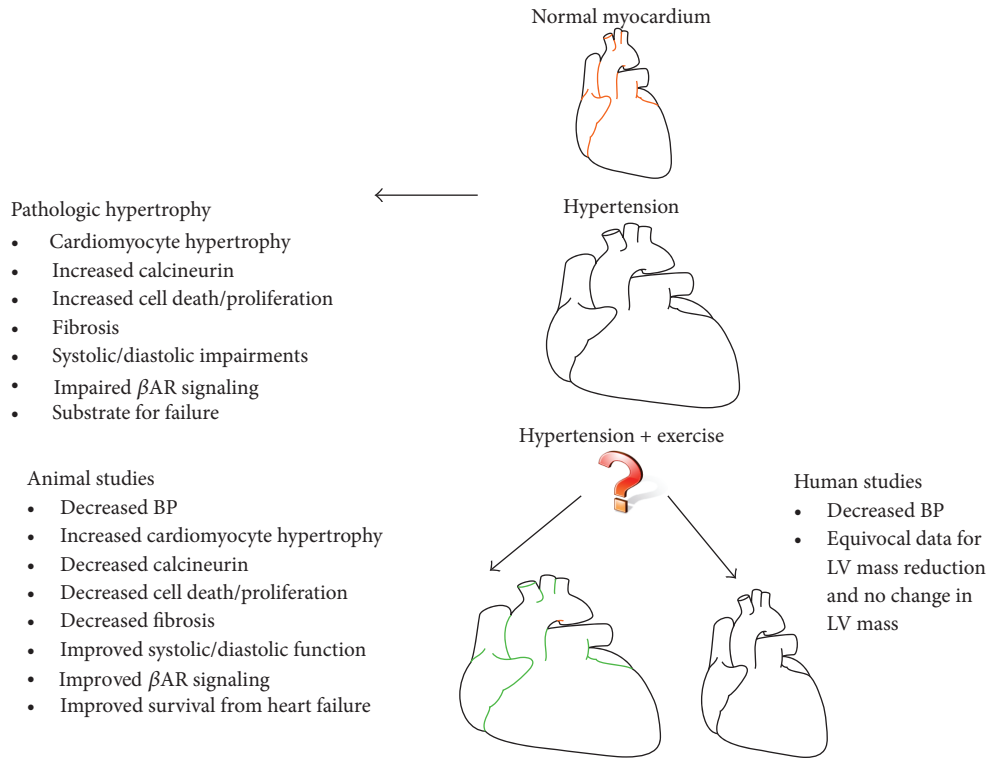

Figure 1: Compensatory pathologic hypertrophy induces cardiac remodeling. Concentric cardiomyocyte hypertrophy via increased calcineurin signaling, increased cell death per cardiomyocyte proliferation, increased fibrosis, impaired cardiac function, and decreased β adrenergic signaling are all hallmarks of compensatory pathologic hypertrophy. Exercise training decreases blood pressure and rate pressure product in hypertension. However, its effects on overall heart remodeling are unclear. Data in humans show an equivocal response with the heart either getting smaller or showing no change. In animal studies, whole heart enlargement with cardiomyocyte hypertrophy occurs, despite a reduction of calcineurin protein expression. Training decreases the cell death/proliferation ratio, decreases fibrosis, and improves the overall phenotype of the hypertensive heart.

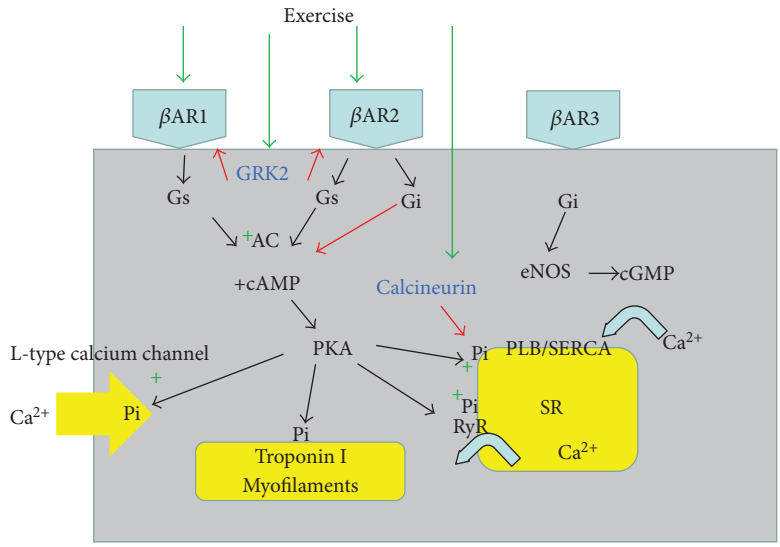

Figure 2: β adrenergic signaling is impaired in hypertensive cardiomyocytes via GRK2 (red arrows). Exercise training attenuates GRK2 and calcineurin abundance in hypertension (green arrows) thereby allowing greater phosphorylation of PKA targets (green $^{+}$) such as phospholamban (PLB), ryanodine receptor (RyR), and the L-type Ca^{2+} channel leading to improved systolic and diastolic functions during stress and exertion. Exercise also alters the agonist binding affinity for βAR receptors (green arrows). SR: sarcoplasmic reticulum; AC: adenylyl cyclase; NOS: nitric oxide synthase; Gs: G stimulatory protein; Gi: G inhibitory protein.

Compensatory concentric hypertrophy is frequently manifested with altered myocardial systolic and diastolic function, for example, increased LV chamber stiffness [16] and fibrosis [15]. Diastolic abnormalities are clinically significant, as diastolic heart failure accounts for nearly one-half of total heart failure cases and significantly increases five-year mortality up to 10 fold [17].

The development of compensated hypertrophy is regulated by mechanical loading factors in concert with the activation of endocrine, paracrine, and autocrine growth factors. These factors activate cardiomyocyte hypertrophic growth by signaling through specific G-protein coupled ligand receptors [18, 19]. These signaling pathways also regulate Ca^{2+} transients in relation to the enhanced afterload of the hypertensive heart. However, chronic activation of these signaling pathways and subsequent chronic elevations in intracellular Ca^{2+} concentrations induces cardiomyocyte growth via Ca^{2+}-calmodulin-related mechanisms [19, 20]. In particular, the Ca^{2+}-calmodulin-activated protein phosphatase, calcineurin, is centrally involved in hypertension-induced compensatory hypertrophy. Activated calcineurin dephosphorylates members of the NFAT transcription factor family in the cytoplasm of cardiomyocytes thereby promoting nuclear translocation and the induction of a fetal gene program [18–22]. Transgenic overexpression of calcineurin has been shown to markedly increase heart size and induce heart failure, whereas calcineurin inhibition prevents these pathological sequences [19, 20]. Both cyclosporine A and FK506 have successfully been used to attenuate the development of cardiac hypertrophy by suppressing calcineurin abundance [18, 21]. Of interest, although calcineurin inhibition arrests cardiac hypertrophy in the face of pressure overload, it does not induce short-term hemodynamic compromise [22]. The development of agonist-induced cardiac hypertrophy with phenylephrine and angiotensin II infusions has also been blunted with various techniques of calcineurin inhibition [23, 24].

2.2. Apoptosis and Proliferation. Compensatory cardiac remodeling with pressure overload is also influenced by the number of functioning cardiomyocytes. Thus understanding the balance between cardiomyocyte proliferation and apoptosis in pressure-induced hypertrophy is important [25]. Several reports have shown that the heart contains resident cardiac stem cells that are capable of generating new cardiac tissue including cardiomyocytes [26–28]. We have recently shown that hypertension slightly increases cardiomyocyte proliferation and the number of c-Kit+ cells in hypertensive rodent myocardium [25]. However, hypertension-induced cell death occurs to a greater extent than cell proliferation, perhaps rendering the hypertensive myocardium with lesser number of functional cells relative to normotensive controls. As my laboratory has shown, the increased ratio of cell death to cell proliferation may also be linked to compromised LV systolic functional performance in the hypertensive heart [29]. Even early in the hypertensive cascade, systolic elastance is lower in hypertensive hearts relative to normotensive controls [29, 30]. Whether this is related to hypertension-induced increases in apoptosis remains unknown, but is important to consider given that apoptosis induces cell shrinkage, membrane blebbing, DNA fragmentation, chromatin condensation, and cell death [31, 32]. The apoptotic death program is triggered by both internal and external signaling pathways. Cell death is typically replaced by fibrosis [33] and is likely associated with the transition from compensated LV hypertrophy to heart failure [34] (Figure 1).

One molecule that is centrally involved in cell survival is protein kinase B or Akt. Akt-mediated phosphorylation of Bad promotes sustained activation of prosurvival factors that induce cell survival by decreasing mitochondrial membrane destabilization and cytochrome c release [35–37]. Akt can also phosphorylate caspase 9 and decrease its activity [38]. The Akt pathway has been shown to be upregulated with aerobic exercise and is linked to physiologic hypertrophy and may provide protection from apoptosis [39–41]. However, it is unclear whether training upregulates Akt in the hypertensive heart [25, 30].

2.3. Downregulation of Cardiac β-Adrenergic Receptors. Of significance, compensatory hypertrophy secondary to pressure overload is associated with a reduction in β-adrenergic receptor (βAR) responsiveness and subsequent altered myocardial inotropic and lusitropic function in response to sympathetic stress [42]. Although some studies have shown a decreased βAR density in hypertension [43], abnormalities "downstream" from the βAR are also involved in the impaired adrenergic responsiveness of the hypertrophied heart. For example, βAR kinase (βARK1 or GRK2) has been shown to be centrally involved in blunting βAR signaling in pressure overload hypertrophy [44] (Figure 2). Moreover, calcineurin-dependent signaling is also involved in βAR downregulation, and recent data have shown that calcineurin opposes protein kinase A (PKA) activity [45, 46]. Our laboratory has shown that the calcineurin antagonism corrects impaired β adrenergic responsiveness in hypertensive hearts [46]. Shifts in β adrenergic responsiveness are also involved in diastolic dysfunction, secondary to a limited PKA-driven phosphorylation of phospholamban.

The βAR pathway is the primary physiological means by which sympathetic stimulation controls myocardial inotropy, lusitropy, and chronotropy. Thus, this pathway is very important in regulating cardiovascular function during stress and exercise. βARs are members of the 7-transmembrane domain receptor family which are coupled to GTP-binding proteins (Figure 2). There are several isoforms of βARs in the heart (βAR1, βAR2, and βAR3). Activation of βAR1s causes bound GDP to be exchanged for GTP and stimulates adenylyl cyclase [47]. The activation of adenylyl cyclase causes an elevation in cyclic AMP and subsequently activates cyclic AMP-dependent PKA. PKA phosphorylates key Ca^{2+} cycling proteins including troponin I, L-type Ca^{2+} channels, phospholamban, and ryanodine Ca^{2+} release channels. The phosphorylation of L-type Ca^{2+} channels enhances Ca^{2+} current and stimulates sarcoplasmic reticulum (SR) Ca^{2+} uptake and release upon being agonized with β agonists. Also βAR1 activation decreases myofilament Ca^{2+} sensitivity

secondary to phosphorylation of troponin I. Activation of βAR also increases cardiac metabolism and glycogenolysis.

Overstimulation of βARs can cause them to become desensitized in seconds to minutes. βARs are found to be downregulated in both hypertension and heart failure which are both conditions of high sympathetic tone [42, 44, 46]. Downregulation of βARs involves the phosphorylation of serine on carboxy-terminal end of the βAR receptor by GRK2 and/or PKA [44, 48]. This can set the stage for βARs to be internalized by β arrestin, with the internalized βARs receptors being either recycled or degraded, leading to impaired inotropic and lusitropic function [49].

βAR2 activation can produce the same effects as βAR1s. However, βAR2s are coupled to both Gs and Gi proteins [50]. Agonism of βAR2 likewise induces a PKA-mediated increase in inotropy and Ca^{2+}; however, their augmentation on cAMP concentrations and phospholamban phosphorylation are not as great as in βAR1 agonism. In heart failure the ratio of βAR1/βAR2 falls and may be related to impaired cardiac performance with stress. Lastly, βAR3 activation induces negative inotropic effects through nitric oxide signaling (NO) [51]. NO production in ventricular myocytes stimulates guanylyl cyclase, cGMP production, and activates protein kinase G. While βAR3s lack serine, they do not appear to be desensitized by GRK2. Agonism of βAR3's has been shown to decrease myofilament Ca^{2+} sensitivity and Ca^{2+} current [52].

3. Exercise Training

3.1. Cardiac Remodeling. Chronic exercise training causes a beneficial adaptive response of the cardiovascular system, that is, decreased resting and submaximal heart rates and increased LV filling time, venous return, and stroke volume [53, 54]. Chronic exercise training has been shown to enhance myocardial diastolic function [55–57], alters calcium uptake in the SR [57], and induces sinus bradycardia [53]. Interestingly, exercise conditioning may potentially reverse diastolic dysfunction-associated pathologic hypertrophy [58] and/or with minimal effects on ischemia/reperfusion injury [59] while also lessening age-associated declines in diastolic function [54].

Exercise training induces physiologic, eccentric cardiomyocyte hypertrophy where cardiomyocytes increase in cell length by approximately 7% [57]. Lengthening of cardiomyocytes causes enlargement of the left ventricular cavity and focal areas of increased wall thickness. Aerobic exercise activates cardiomyocyte growth by stretch via increased plasma volume as well as activation of growth signals like insulin-like growth factors [39, 40]. It should be appreciated that there is a good correlation between left ventricular function during diastole and aerobic fitness [60]. Exercise-induced cardiac remodeling has not been typically shown to increase interstitial fibrosis. Some reports even suggest that exercise training can reduce the development of fibrosis in established pathologic hypertrophy [61]. However, a very recent paper has shown that high levels of wheel running velocity in SHR rats can induce a profibrotic phenotype and is positively correlated with LV mRNA of TGF-β1, collagen III, and biglycan, whereas wheel running velocity was negatively correlated with SERCA2A to Na^{+}-Ca^{2+} exchanger ratio [62].

The effects of exercise training on cardiac remodeling in hypertensive human subjects have been reviewed elsewhere [63] and have shown equivocal results with some studies showing no change in left ventricular mass [64–69], a decrease in left ventricular mass/left ventricular mass index [64, 70–74], and an increase in left ventricular mass/left ventricular mass index [5, 66]. The majority of these studies showed that systolic and diastolic blood pressure was reduced following exercise, and imaging was most often measured with M-mode and 2D guided echocardiography. These studies also suggest that exercise can potentially reduce left ventricular mass, independent of the blood pressure lowering effects of exercise [68]. Disparities in results concerning LV hypertrophy following exercise training may be secondary to variations in study designs, subject characteristics, exercise paradigms, and medication use.

In hypertensive animal studies, exercise training has been shown to reduce or delay the development of hypertension [75]. Voluntary activity wheel running has been shown to reduce sympathetic tone and also results in resting bradycardia and attenuation of the tachycardia response during progressive exercise in SHR [76, 77]. This effect can, in part, be attributed to a significantly reduced adrenergic tone controlling heart rate during exercise [78].

However, even though chronic exercise training reduces heart rate and blood pressure, it has been shown to increase hypertrophy at both the whole heart and cellular level in laboratory animals [25]. Our laboratory has reported whole heart hypertrophy with echocardiography and histomorphometry with exercise training that is dispersed across several walls of the left ventricular myocardium (anterior, posterior, and septal walls). Isolated cardiomyocytes from exercise trained SHR were both longer and wider relative to sedentary controls [25]. Similar findings in swim-trained animals have been reported, such that swim training increased left ventricular weight and left ventricular internal diastolic diameter in the spontaneously hypertensive rats [61]. Swimming also increased cardiomyocyte cross-sectional area, reduced apoptosis, and normalized calcineurin without any significant changes in the Akt pathway. This led to reduced fibrosis, improved vascularization, and enhanced fractional shortening on echocardiography [61]. Thus even though exercise potentiates cardiomyocyte growth, cardiac function is enhanced relative to sedentary controls.

Our studies have also found that training mitigated calcineurin gene and protein expression in hypertension [30], illustrating that exercise superimposed on hypertension induces cell growth by other signaling mechanisms beyond Akt [25]. We have also reported a reduction in overall cell death with training, despite an increased expression of caspase 3 in hypertensive trained hearts [30]. This is similar to recent data by Huang et al. who showed a reduction in Fas ligand and mitochondrial-mediated apoptosis in SHR following training [79]. We have also found that the rate of cardiomyocyte proliferation is increased with training and

hypothesize that training may beneficially preserve overall cardiomyocyte number and phenotype in hypertension [25]. Thus one of the major benefits of exercise training in hypertension is the preservation of cardiomyocyte cell number. Despite the potential for exercise training to increase myocardial mass in pressure overload, most studies have reported an improved phenotype after training [25, 30, 46, 61, 80–87]. One of the most prolific benefits of exercise training is its improvement on adrenergic signaling.

3.2. β-Adrenergic Responsiveness. Studies in both normotensive and hypertensive humans and animals have shown that exercise training enhances βAR responsiveness [46, 88–112] throughout the lifespan. One study in postmenopausal women did not show a putative effect in βAR responsiveness with training [90]. Interestingly, a study by Scott et al. showed that postexercise βAR responsiveness was maintained in women to a greater extent than men following exhaustive exercise. This is a significant finding given that postexercise βAR desentization is hypothesized to be an element of cardiac dysfunction after acute, exhaustive exercise [112].

While treadmill running is typically used as the exercise modality, swimming has also been shown to be effective in increasing βAR responsiveness in increasing agonist-binding affinity and increased βAR responsiveness, despite a reduction in myocardial βAR density [94]. While βAR binding affinity has also been shown to increase following training [107], such findings iterate the importance of downstream signaling adaptations with training [46, 81].

In general, cardiac βAR density has been shown to decline with exercise training without changing the ratio of βAR1 to βAR2s subtypes [96–98]. Still other studies have shown an attenuation of βAR1s with training without altering βAR2s. Conversely, Stones et al. showed that βAR1 inotropic responsiveness was not changed following voluntary wheel running. However, βAR2 specific adrenergic inotropic responses were attenuated in trained animals [92]. Exercise training has also been reported to attenuate the contractile responses to βAR2 stimulation in dogs while restoring βAR1 adrenergic receptor protein content [99–101]. Whether training exerts its effects on downregulating βAR2s is an interesting idea that requires further testing.

Our work in SHR animals has shown that despite the induction of hypertrophy with treadmill running, exercise improved βAR responsiveness by attenuating the characteristic rise of GRK2 in the hypertensive heart [46]. Iemitsu et al. also showed that GRK, BMP, ACE, and ET-1 mRNA were reduced in swim-trained SHR rats compared to SHR sedentary animals [85]. Exercise training has also been shown to alter PKA-mediated phosphorylation of key calcium handling proteins such as the ryanodine receptor and phospholamban [46]. Our studies have also shown that exercise training potentiates the inotropic responses to forskolin [81]. This is consistent with other studies showing that adenylyl cyclase activity increases with exercise. Exercise training has been shown to increase adenylyl cyclase activity in the absence of a βAR agonist [102] or in the presence of a βAR agonist [110]. There are, however, data that show no change or even a decrease in adenylyl cyclase activity with training [102, 103]. Thus exercise training improves βAR responsiveness in hypertension, but the underlying mechanisms have not been fully elucidated. A reduction in GRK2 and calcineurin with training in hypertension have been shown to be mechanistic component of the adaptive response [46, 85, 105, 106] (Figure 2).

Beyond improved βAR responsiveness with training in hypertension, exercise has generally been shown to improve the overall heart phenotype and prolong survival [86, 87]. While extreme levels of acute and chronic exercise may be deleterious to the heart by increasing apoptosis, fibrosis, and ischemic dysfunction [62, 113, 114], moderate levels of exercise seem protective from cardiac damage. These animal studies support the American College of Sports Medicine recommendation for encouragement of exercise on most, if not all, days of the week, at moderate intensities, by accumulating 30 minutes or greater of endurance-style physical activity [7].

4. Summary

Compensated left ventricular hypertrophy in hypertension involves cardiomyocyte hypertrophy, apoptosis, and proliferation of cardiomyocytes. Exercise affects each of these pathways, but the contributory role of specific signaling pathways is not clear. Calcineurin expression is attenuated with exercise training, but in animal studies, exercise instead increases cardiomyocyte hypertrophy while decreasing apoptosis and fibrosis. High volume/intensity exercise in hypertension, however, may be deleterious to the heart by increasing apoptosis and cardiac dysfunction. In humans, exercise training shows equivocal morphometric results, with some studies showing a reduction in LV mass and others no change. In both humans and animals, exercise improves the overall phenotype of the heart. This effect appears to be independent of the blood pressure lowering effects of exercise. One of the hallmark phenotypical shifts with hypertension is a downregulation of the βAR system. Exercise training improves βAR responsiveness in the heart, perhaps by increasing βAR binding affinity or through downstream effects such as a suppression of GRK2 and calcineurin. Despite the underlying mechanisms, participation in exercise and physical activity is important for prehypertensive and hypertensive patients and should be performed at low intensities. Patients should closely consult with their healthcare providers in structuring an exercise program.

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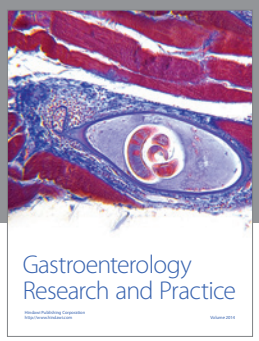

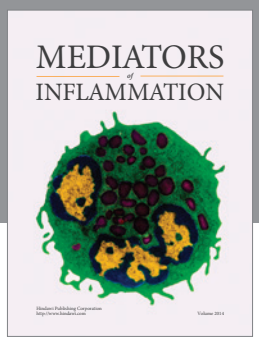

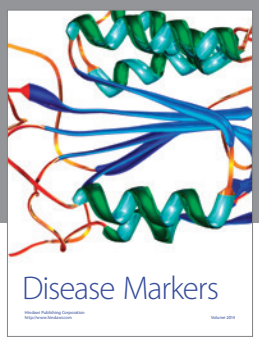

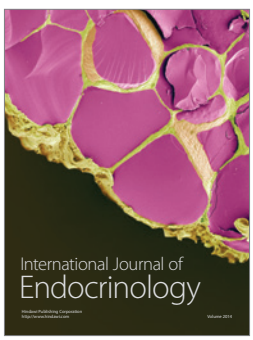

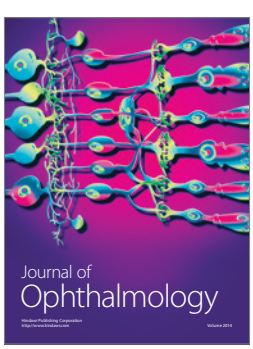

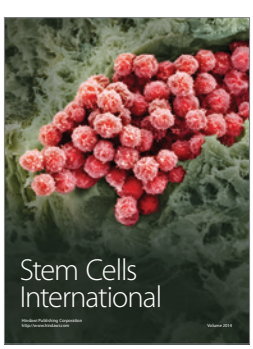

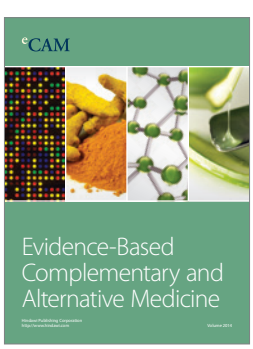

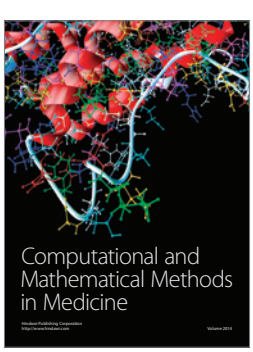

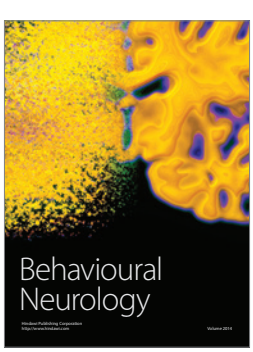

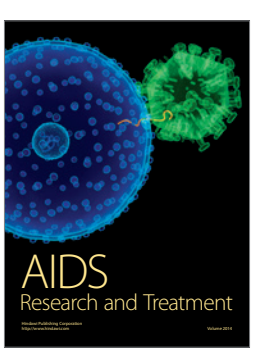

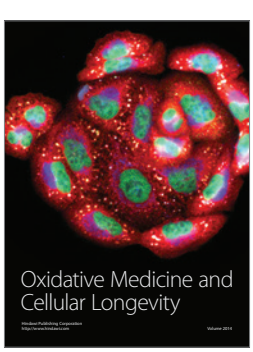

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