

# **Aerobic Exercise Does Not Predict Brain Derived Neurotrophic Factor And Cortisol Alterations in Depressed Patients**

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**Abstract:** The pathophysiology of depression is related to neurobiological changes that occur in the monoamine system, hypothalamic-pituitary-adrenal axis, neurogenesis system and the neuroimmune system. In recent years, there has been a growing interest in the research of the effects of exercise on brain function, with a special focus on its effects on brain-derived neurotrophic factor (BDNF), cortisol and other biomarkers. Thus, the aim of this study is to present a review investigating the acute and chronic effects of aerobic exercise on BDNF and cortisol levels in individuals with depression. It was not possible to establish an interaction between aerobic exercise and concentration of BDNF and cortisol, which may actually be the result of the divergence of methods, such as type of exercises, duration of the sessions, and prescribed intensity and frequency of sessions.

**Keywords:** Aerobic exercise, biomarkers, brain derived neurotrophic factor, cognition, cortisol, depression.

## **INTRODUCTION**

Depression is related to several neurobiological changes [1, 2]. Research on the possible molecular pathways of depression demonstrated that the increased cell dysfunction in cortical and limbic areas of the brain can be observed in individuals suffering from depression [3, 4] and is strongly related to the decrease in neurotrophic activity [5]. Therefore, the investigation of biomarkers, such as brain-derived neurotrophic factor (BDNF), has attracted great interest, in order to clarify its role in the pathophysiology of depression [6]. BDNF is a protein expressed mainly in the central nervous system (CNS), and it has an important role in the survival and maintenance of neuronal function [7]. In fact, a low neurotrophic activity is associated with reduced numbers of cells in the prefrontal cortex [8], amygdala [9, 10] and a decrease in hippocampal volume [11, 12], indicating that the growth nerve factors, and more specifically, the changes in BDNF may play an important role in the development of depression [3, 4, 13-15]. Furthermore, the dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis has been the most valid neurobiological theory to explain the pathophysiology of depression. The HPA axis is the interaction between the hypothalamus, pituitary gland, and the adrenal cortex, and is a major part of the neuroendocrine system that controls reactions to stress [16]. The clinical manifestation of its dysfunction in depression includes basal hypercortisolemia [17], elevated cortisol secretion in the dexamethasone suppression test [18], and increased cortisol release in the combined dexamethasone suppression-corticotropine releasing hormone stimulation test [19, 20]. The first line of treatment for depression is the use of antidepressants [21]. However, the remission rate with selective serotonin reuptake inhibitor (SSRI), which is currently the first-line treatment for depression, is only 60% [22]. Exercise is a readily available therapeutic option, effective as a treatment in mild to moderate depression [23]. Regular exercise may bring

physiological, psychological and social benefits to its practitioners [24-26]. Given that sedentary is a recognized risk factor [23] for many diseases, exercise has become a topic of great interest to many researchers. Thus, the practice of exercises has been increasingly recommended in health promotion programs by institutions such as the Center for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) as a non-pharmacological means of prevention and treatment of psychiatric disorders such as depression [27, 28]. The effectiveness of exercise on depression has been attributed to its impact on the modification of certain neurobiological mechanisms such as: influence on monoamine metabolism by increasing serotonin levels; regulating function of the HPA axis, with possible reduction in cortisol secretion; increase in neurotrophic factors such as BDNF and hippocampal neurogenesis and, finally, reducing neuroinflammation through a decrease in proinflammatory mediators [29-38]. Ida et al. [21] examined the acute effects of aerobic exercise performed in cycloergometer in the salivary cortisol levels as well as the scores of subjective symptoms of depression in patients diagnosed by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The salivary cortisol levels were measured pre-exercise and postexercise. The same patients returned after a month for a control session (sitting quietly), where the salivary cortisol levels were measured pre- and post-session. The authors concluded that a session of 15 minutes of moderate intensity aerobic exercise could reduce salivary cortisol levels. In addition, a decrease in salivary cortisol level was statistically correlated with a decrease in the scores of subjective symptoms of depression. It is noteworthy that all patients were being treated with antidepressant medications during the study, and in addition, subjective depression scores used in this study have not yet been validated on a large scale. A new view on the benefits of regular practice of physical exercise has been discussed in some studies that show the anti-inflammatory effects of exercise [21, 39]. There is evidence that shows that exercise performed at a moderate intensity may be an important factor in prevention and treatment, not only of metabolic diseases [26, 40, 41], but also of symptomatology and cognitive function in mood disorders [42, 43], although its physiological effects still remain uncertain. Thus, in recent years there has been increasing interest in research on the effects of exercise on brain function, with a special focus on its effects on BDNF, cortisol and other biomarkers [44]. This study aimed to review the acute and chronic effects of aerobic exercise on BDNF and cortisol levels in depressed patients. Here, we will review the basic foundation of BDNF and cortisol, their role in healthy and depressed people and the experimental advances of aerobic exercise on BDNF and cortisol in depressed patients that can become viable as clinical applications in the coming years for major depression (MD). A literature search was conducted using the databases PubMed, ISI Web of Knowledge and PsycInfo using the following terms and their combinations: "aerobic exercise", "depression", "brain derived neurotrophic factor", "cortisol", and "biomarkers". All articles were published between 1995 and 2015 and in English. Additional references were identified through hand search of the possessed articles.

**BDNF: ISOFORMS AND RECEPTORS** The neurotrophic growth factors, known as neurotrophins, are proteins whose main function is the development of neurons, contributing for their survival, growth and characterization [45, 46]. The family of neurotrophins includes the nerve growth factor (NGF), the neurotrophic growth factor derived from the BDNF, the neurotrophin-3 (NT-3) and the neurotrophin-4/5 (NT-4/5) [45, 47]. Their biologically active forms show about 50% amino acid identity. The genes encoding neurotrophins are expressed not only during development but also in the adulthood, in a variety of tissues, including the CNS [48]. Neurotrophins sustain the neuroplasticity (i.e., ability of the CNS to adapt to environmental

changes, respond to injury and acquire new information, modifying neural connectivity and function) and are capable of signaling neurons to survive, differentiate, or grow [49, 50]. Neurotrophins interact with two distinct classes of receptors [47]. The first to be discovered was the neurotrophin receptor 75 p-(p-75NTR) [51, 52], which belongs to the family of receptors of the tumor necrosis factor (TNF) [47]. The second class of neurotrophin receptors includes the receptors for tropomyosin-related kinase (Trk, tyrosine kinase). All neurotrophins bind to the receptor p-75NTR, but neurotrophins bind with greater affinity to its specific receptor Trk [52]. In particular, NGF binds to TrkA, BDNF and NT-4/5 bind to TrkB and NT3 binds with greater affinity to TrkC [53]. Among these neurotrophins, BDNF has attracted great interest as a functional candidate gene in several mental disorders. The BDNF gene is located on chromosome 11p13 reverse strand and encodes a precursor peptide pro-BDNF [54]. In fact, all neurotrophins, including BDNF, are synthesized as a pre-pro neurotrophic precursor. In particular, pro-BDNF preferably activates p75NTR to mediate the programmed neuronal death [55], to reduce the complexity and density of the dendrites of hippocampal neurons [56] and to induce long-term depression of synaptic transmission [57, 58]. The function of a receptor for BDNF (i.e., TrkB) is also regulated in an activity-dependent manner, as TrkB is mainly located in synapses. In addition, BDNF can be found in synapses after neuronal activity [59]. The neuronal activity, however, is essential for the synthesis and intracellular targeting of TrkB receptors. Thus, the release of BDNF and TrkB receptors expression in a coordinated manner are important for optimal synaptic response [60].

#### BDNF: ISOFORMS AND RECEPTORS

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neuronal activity [59]. The neuronal activity, however, is essential for the synthesis and intracellular targeting of TrkB receptors. Thus, the release of BDNF and TrkB receptors expression in a coordinated manner are important for optimal synaptic response [60].

#### THE ROLE OF BDNF AND CORTISOL IN HEALTHY HUMANS

BDNF, which is an essential neurotrophin connected directly to the central and peripheral molecular processes of energy metabolism and homeostasis, may play a key role in these induced mechanisms [61]. BDNF has a repertoire of neurotrophic and neuroprotective properties in the CNS and the periphery [62- 64]. The effect of BDNF on the plasticity of the CNS involves elements of cellular energy metabolism and in the periphery participates in metabolic processes. Prime examples come from studies of transgenic mice heterozygous for BDNF, which suffer from hyperphagia, obesity and hyperinsulinemia [65, 66]. Tonra [67] demonstrated that central or peripheral administration of BDNF reduces body weight and improves glycemic control in obese diabetics. BDNF also appears to be a positive regulator of energy expenditure, and BDNF has shown to be effective in preventing reduction in body temperature during cold exposure or food deprivation [68]. Furthermore, Wu et al. [69] reported that increase in oxidative stress, which would be a consequence of aberrant energy metabolism, result in decreased BDNF levels. BDNF works toward neuronal protection and survival, axonal and dendritic growth and remodeling, neuronal differentiation and synaptic activity (synaptogenesis) and has efficacy in synaptic transmission [70, 71]. In the periphery, BDNF function is to increase lipid oxidation in skeletal muscle through the activation of activated kinase protein (AMPK) [72]. A human case study showed a clinical phenotype of impaired cognitive function, hyperactivity and severe obesity associated with a chromosomal inversion of a region encompassing the BDNF gene, and a reduction in serum BDNF [73]. Furthermore, Araya et al. [74] demonstrated that plasma BDNF was increased in insulin resistant individuals, overweight subjects and obese subjects following a reduced-calorie diet. These findings reinforce the fact that BDNF is essential not only in the neuronal system, but are also strongly linked to the central and peripheral molecular processes of energy metabolism and homeostasis [75, 76]. With regard to cortisol, which is released by the cortex of the adrenal gland, it is the main glucocorticoid to be directly involved in the regulation of plasma glucose [77]. Glucocorticoids are widely distributed in the brain, specifically concentrated in the hippocampus, amygdala and hypothalamus [78]. Cortisol is not only part of the circadian system, but helps to organize it. Corticosteroids act on the glucocorticoid and mineralocorticoid receptors [79]. Steroids also act over receptors linked to genomic membrane, which may play a role on neuronal function [80]. HPA axis responds quickly to a range of environmental and internal factors, which are often associated to stress [16]. Although cortisol performs a feedback function at the level of the pituitary gland, hypothalamus and hippocampus, prolonged stress can stimulate secretion over several hours. After stimulation by adrenocorticotropin (ACTH), cortisol is synthesized and secreted by the adrenal gland and released into the blood, circulating quickly on carriers such as corticosteroid-binding globulin, albumin and erythrocytes. Only a small fraction of cortisol (2-15%) remains free. It is just that fraction of free hormone that causes the multitude of cortisol related genomic effects in peripheral tissues and the brain [81]. It is also known that about 30 to 60 minutes after awakening, there is an increase in cortisol secretion [82], but the area or the type of receptor that may be involved in the risk posed by this change has not yet been established [83].

## THE ROLE OF BDNF AND CORTISOL IN DEPRESSION

The pathophysiology of depression has been associated with dysregulation of the HPA axis [84]. Hyperactivity of the HPA is one of the most robust and consistent neurobiological findings in patients with MD, and cortisol have been suggested as a potential biomarker of this disease [85, 86]. The cortisol contributes to genetic variants increasing the risk of developing MD, so that environmental events may extend such a risk. The influence of corticosteroids begins prenatally, but continues during adulthood. The impact of cortisol in each phase depends not only on their interaction with other factors, such as psychological traits and genetic variants, but also on the events that have or not previously occurred [87]. There is little doubt that cortisol plays a central role in the onset and course of depression, but there is still considerable uncertainty about what exactly that role is [87]. The daily cortisol rhythms are disturbed in about half the cases of MD [88]. There is an increase of resistance to the action of glucocorticoid feedback on the HPA activity in a proportion of cases of DM [89, 90]. The post-awakening cortisol increase and prolonged excessive levels can result in DM [91-96]. Cortisol levels in excess can put the brain at risk, making it more vulnerable to harmful agents that in the absence of corticoids would not necessarily be harmful [97, 98]. This notion can be translated to the MD, since that adversity predisposes to this disorder [99, 100], and increased cortisol can potentiate the psychopathological actions of these agents in a similar way [101]. The development and maintenance of the vertebrate nervous system requires continuous operation of a number of proteins called neurotrophins. It has been shown that in the adult brain occurs the proliferation and maturation of neurons in discrete areas including the hippocampus and the striatal subventricular area. Exposure to psychotropic substances or stressors mediates the process of adult neurogenesis by regulating the expression and function of some growth factors, suggesting a possible role of neurogenesis in the pathophysiology of MD [102, 103]. The physiological role of BDNF is to stimulate the development and stabilization of connections between neurons. This growth factor influences the expression levels of reelin, a molecule of the extracellular matrix that plays an important role in the processes of neural plasticity in important areas for plasticity and memory, such as the hippocampus and cortex, as well as other components of the limbic system and amygdala [104]. Furthermore, both BDNF as well as glutamate are involved in the process of synaptic plasticity, neurogenesis and neural survival in the adult brain. In fact, both signals are co-regulated: glutamate stimulates the expression of BDNF, so that there is an increase in the growth and survival of glutamatergic neurons [105]. There is much evidence of a possible validity of BDNF as a biomarker of MD, as follows: low levels of this marker in the blood of depressed individuals; a negative correlation between blood levels of BDNF and Hamilton scale score of patients with depression; as well as increases in hippocampal BDNF expression in subjects treated with antidepressants compared to healthy controls [106, 107]. The basic assumption is that MD is caused by a maladaptation to the plasticity of the brain, and antidepressants act allowing renewed plasticity that somehow restores normal function [108]. Exactly where and how this occurs and how could explain the MD was not specified, although the hippocampus is an obvious target in this process, which contains high concentrations of both BDNF and its main receptor, TrkB.

## THE EFFECT OF AEROBIC EXERCISE ON THE PLASMA OR SERUM CORTISOL CONCENTRATIONS IN DEPRESSIVE PATIENTS

Few studies have analyzed the relationship between serum cortisol levels and aerobic exercise in patients with depression [21, 32, 109-112]. Krogh et al. [109] investigated whether an exercise

intervention for four months could change the hormonal response to acute exercise in depressed patients. The study consisted of two phases. In the first phase (i.e., acute), were recruited 44 healthy individuals (GC), without physical and mental disorders, who did not practice any physical activity for more than an hour a week, and had anthropometric characteristics corresponding to those of depressed patients ( $n = 137$ ). The responses of serum growth hormone (GH), prolactin and cortisol in depressed patients were compared with GC, adopting an incremental test on a cycloergometer as exercise for patients. After that (i.e., 2nd phase), the responses of these hormones after 4 months of intervention using three different exercise modalities in depressed individuals were investigated. Randomization was centralized and stratified according to antidepressant medication: 1) have not received any antidepressant medication; 2) have received an antidepressant medication for less than six weeks and 3) have received an antidepressant medication for more than six weeks. The sample consisted of 137 adults with MD ( $38.9 \pm 9.6$  years) and 44 adult control subjects ( $38.2 \pm 10.2$  years). For the chronic study (second stage), the sample was divided as follows: relaxation ( $n = 28$ ); aerobic ( $n = 31$ ); and strength training ( $n = 29$ ). All groups underwent their activities twice a week. All groups were divided into age: relaxation ( $36 \pm 9.8$  years); aerobic ( $39.3 \pm 9.8$  years) and strength training ( $42.4 \pm 9.5$  years). However, the control group consisted of healthy subjects who did not use antidepressants. Aerobic training group consisted of a circuit of cyclical activities, which involved large muscle groups. Strength training group consisted of ten exercises using machines and free weights. Relaxation exercises group consisted of stretching exercises prescribed as a way of socializing, at a low intensity. Results showed that there were differences in cortisol response to the incremental test among groups, where the group of healthy subjects showed higher concentrations in serum. However, at the end of the four month intervention, no difference was found in baseline values of the hormones investigated among the three groups, as well as there were no significant changes in cortisol levels after the incremental test on cycloergometer. It is well described that in times of stress, there is increased secretion of cortisol. Therefore, the difference found in the incremental test may have happened because the depressed group makes use of antidepressant medication, which may have influenced an increasing nonproportional to the effort. Although authors found no evidence for greater variation due to use of antidepressants, this could be considered as a limitation of the study, since these medication have chronic effects on the HPA axis and monoamines. Nabkasorn et al. [32] investigated the effect of exercise on depressive state, in the concentration of cortisol in urine and physiological variables of fitness. The study was carried out on samples without a clinical diagnosis of depression, but with some symptoms, while the studies of Krogh [109], Garcia [110], Wied [111] and Kiive [112] were conducted on clinical samples. The study included 49 female adolescents ( $18.8 \pm 0.7$  years) with mild to moderate depressive symptoms. The exercise protocols consisted of recreational activities and training. The sample was divided into two groups. The group A began with the eight-week training, and group B participated only usual activities, serving as a control. After eight weeks, there was a reassessment. After this procedure, there was alternation of activity between the groups, with group A began performing recreational activities and group B began performing training. In the training protocol, the exercise performed was running at a lower intensity than 50% of maximum heart rate reserve. The group that began the study with recreational activities and then was moved to training showed a higher decrease in the concentration of cortisol in urine than the other group. However, data showed a significant decrease in the concentration of cortisol in the urine in both groups after 16 weeks compared to pre-intervention period. Perhaps because the group B was the last receiving training, may have showed a greater training effect on the studied variables. The limitation of this study was not having used a structured psychiatric interview to assess the

individuals, which were classified with mild to moderate depressive symptoms by Center for Epidemiologic Studies Depression Scale (CESD). This instrument is a self-report scale, widely used as a screening tool, especially used in primary care and outpatient, but represent the symptoms over the previous week and may include more transient or temporary symptoms than other measures. In addition, five individuals of the group who started with training participated of an exercise class again in the period in which no exercise was scheduled. Thus, these individuals were excluded of the data analysis in order to do not influence the results of this group after training. At last, the sample consisted of female adolescents without clinical depression and these results cannot be generalized to other populations with different ages and different levels of depressive symptoms. Thus, it is important to highlight the role of chronic exercise on this marker in depressed patients. It appears that regular exercise can influence long-term treatment of MD. Garcia et al. [110] evaluated serum cortisol levels response to the incremental cycloergometer test. The study included 43 adults, 23 of which belonged to the depressed (mild and moderate) groups ( $43.5 \pm 1.8$  years). Fourteen participants had mild depression and 9 moderate depression. The 20 individuals in the control group ( $42.8 \pm 3.0$  years) were healthy. At baseline, serum cortisol levels were significantly lower in both groups of depressed, compared to the control group. Immediately after exercise, and also thirty minutes later, both the control group and the mild depression group had higher levels of cortisol, while the group with moderate depression remained with lower cortisol levels. At 90 minutes after exercise, the control group and the patients with moderate depression showed a reduction in cortisol levels in relation to levels of cortisol peak, which was amended in individuals with moderate depression. It seems that just an exercise session is not enough to influence positive adaptations in cortisol levels, considering that this session also led individuals to exhaustion, resulting in greater metabolic stress. It is known that the use of antidepressants can influence on different responses of cortisol in patients with depression, and an important limitation in the study was because the authors did not describe whether depressed patients used antidepressant medication. Therefore, we need to know whether this finding applies to severe depressed who do not use antidepressant medication. In another experiment, Wied et al. [111] sought to determine whether depressive symptoms affect the pituitary-adrenal function in adolescents. The study included 36 subjects, including 23 hospitalized adolescent psychiatric patients (10 depressed e 13 non-depressed), of both sexes, belonging to the intervention group ( $15.8 \pm 1.7$  years). The control group consisted of 13 adolescents ( $16.9 \pm 1.4$  years) who underwent physical exercise for ten minutes on a stationary bike. Two samples of salivary cortisol were collected before the test, and four samples were taken after testing, at intervals of 20 minutes. In the intervention group, cortisol profiles were evaluated at two-hour intervals before and after administration of dexamethasone and hydrocortisone. There were no differences in basal cortisol levels between depressed and non-depressed groups. This study had important limitations. Among them, we can highlight that were compared two different types of cortisol response analysis (i.e., exercise in the control and suppression of dexamethasone and hydrocortisone in the experimental group). It was also not described the intensity that exercise was carried out on cycloergometer in the control group, either if these individuals had familiarity with the adopted ergometer and were physically active. It is known that trained and untrained individuals may have different magnitude of hormonal responses. It can also be noted that depression and dysthymia can cause different responses of HPA axis, and some individuals of the depressed group had dysthymia. Other relevant point is, the level of depression was not described, and a subjective classification of levels of depression was performed using a self-report scale (SCL-90). In addition, the sample consisted of adolescents with enough variety of comorbidities and then, this study cannot be applicable to depressed adults. Kiive et al. [112]

compared the responses of serum GH, prolactin and cortisol to cardiopulmonary cycloergometer test in depressed patients and healthy subjects. The study involved 46 adult males, including 24 depressed patients ( $43.5 \pm 1.8$  years) and 22 healthy volunteers ( $42.8 \pm 3.0$  years). The control subjects and the depressed patients did not differ significantly in age, height, weight, or body mass index. The results showed an increase in cortisol secretion in response to acute exercise in both groups, but there was no significant difference in the concentration of this hormone between them. Therefore, the authors reported that the sample was small to allow a conclusive statistical analysis. Still, this experiment also led individuals to exhaustion, causing stress and expected elevation of cortisol. It would be interesting to apply an exercise protocol in lower intensities and chronic manner, so that possible differences could be found in the concentrations of this hormone between groups. Another possibility for failing to find any differences in cortisol responses between groups is that the patients used different drugs, where two outpatients did not report the use of antidepressant drugs, six patients were treated with tricyclic antidepressants (i.e., clomipramine, nortriptyline), eight patients with SSRI-s (i.e., fluoxetine, paroxetine, citalopram), three patients with mirtazapine and one patient with moclobemide. Four patients reported the use of antidepressants, but the type was not specified. Another limitation was no description of the level of depression, apart from the fact that patients were at different stages of treatment. Ida et al. [21] investigated the influence of an aerobic exercise session in cycloergometer for 15 minutes on salivary cortisol levels in depressed individuals. One month later, patients were invited to a control session where they sat quietly. If patient were using antidepressants before the entry, the dosage was fixed up to the end of the study. Salivary cortisol levels of each participant and the subjective scores of depressive symptoms were recorded before and after both sessions in order to examine the effect of exercise on depressive symptoms. One month after the exercise session, three participants drop out of control session. Both sessions had the same duration and were conducted in the same time of day. Seven patients were in clinical remission, ten had mild symptoms and one had moderate symptoms of depression. It is noteworthy that 17 out of 18 patients were physically active, but most (i.e., 12 patients) walking. Depressed patients who participated in the study were in remission or in mild depressive state. However, they did not have a good quality of life due to chronic depression. The level of salivary cortisol and depressive symptoms decreased significantly after the exercise session. In addition, changes in these variables were significantly positive. Furthermore, although subjective depressive symptoms had improved in the control session, the level of salivary cortisol did not change. However, this study had some limitations. First, the sample size was small and all patients were treated, and depressive symptoms varied among the study sample. Studies with patients free of antidepressants are necessary to avoid possible effects of medication on salivary cortisol concentrations. Another important factor is that patients were mostly in remission and had a mean of 61 months of disorder, and individuals treated with aerobic exercise at disease onset, suddenly, may have different responses from chronic individuals. Second, the scores of subjective depressive symptoms, assessing the change of subjective depressive symptoms, during the procedure were not sufficiently validated and should be confirmed in a future study with a larger sample size. In addition, it was not used any counterbalanced method to control the effects of order. Finally, perhaps the exercise protocol runtime has been insufficient to promote positive effects on cortisol changes (i.e., 15 min). Therefore, it is important the application of protocols to investigate the chronic effects of exercise on salivary cortisol concentration. As well as the perception of effort had been relatively low, perhaps activities performed in other intensities can promote distinct results. Perhaps because most studies have used a protocol of the incremental test [109-111], there were not found positive influences of exercise on cortisol. Nevertheless, studies that adopted the chronic form of

exercise [32, 109] were different in the gender of the samples (male and female), in the age of the participants (adolescents and adults), in the levels of depression, and had a variety of instruments used to classify the disease and different exercise protocols. However, they applied the same intervention period (16 weeks). While Krogh et al. [109] found no influence of chronic aerobic exercise on the concentration of cortisol, Nabkasorn et al. [32] found a positive influence of chronic aerobic exercise on the concentration of this hormone. It is worth noting that the collection methods of cortisol were also different. While Krogh et al. [109] analyzed the plasma cortisol concentration, Nabkasorn et al. [32] analyzed the concentration of cortisol in urine. However, as mentioned above, the study by Nabkasorn was carried out on a nonclinical sample, i.e. without diagnosis of depression, while the ones by Garcia [110] Kiive [112] Krogh [109] and Wied [111] were carried out in clinical samples. Thus, further studies are needed so that the influence of aerobic exercise can be established in the concentration of cortisol in patients with depression.

#### THE EFFECT OF AEROBIC EXERCISE ON THE PLASMA OR SERUM BDNF CONCENTRATIONS IN DEPRESSIVE PATIENTS

There are few studies that analyzed the relationship between serum BDNF levels and aerobic exercise in patients with depression [113-117] (for review, see Tables 1 and 2). Gustafsson et al. [113] evaluated the response of plasma BDNF during incremental cycloergometer test. The study included 36 adult individuals of both genders, with 18 in the control group (34.5 years) and 18 belonging to the group with moderate depression (33.5 years). The depressed group did not use any type of antidepressant. The incremental test was performed with constant load period (six minutes) plus load increments every 30 seconds, until exhaustion. Serum BDNF levels were collected at the following times: pre-test; during the test, on the submaximal and maximal occasions; in the 30 and 60 minutes after completion. There was no difference in plasma concentration of BDNF in any of the moments between the two groups. However, it was observed an increase in BDNF concentration at 60 minutes after the end of the test, when compared to baseline, in depressed patients only. The same response did not occur in the control group. Thus, it appears that a single session of exercise cannot change the concentration of BDNF during acute exercise, exerting influence only 60 minutes after completion. Interestingly, BDNF levels at baseline did not differ between depressed patients and healthy controls, though other findings showed differences in plasma BDNF between depressed patients and healthy subjects [14, 118, 119]. Aiming to investigate the relationship between one exercise session and plasma levels of BDNF, Laske et al. [114] studied 55 adult women, 35 of which were depressed ( $61.1 \pm 7.2$  years) and 20 were healthy ( $58.9 \pm 6.6$  years). The exercise protocol chosen was the incremental treadmill test with an initial speed of 3km/h and load increments every three minutes. Blood samples were collected before the test, at the end of the test, and 30 minutes after completion. There was a significant increase in plasma BDNF right after finishing the test in depressed patients compared to pre-test and 30 minutes after completion. This decrease in plasma levels of BDNF at 30 minutes after the test showed that an exercise session seems to be able to promote a chronic expected increase in concentration of this biomarker. However, these patients were women with moderate to severe depression in clinical remission. Thus, it is necessary to investigate whether patients with different degrees of depression, of both gender and other age range would respond the same way to this intervention. Nevertheless, depressed patients who participated in this study used antidepressants, which could be a bias with respect to the role of exercise on the BDNF concentration. Zoladz et al. [120]

showed that after five weeks of aerobic exercise performed on a bicycle, and not just an incremental session, there was an increase in basal levels of BDNF in young healthy men and women. Thus, it appears that regular exercise plays an important role in plasma BDNF; however, the acute exercise does not influence significantly the levels of this biomarker. Toups et al. [115] compared the plasma concentrations of BDNF in two groups of subjects with moderate depression, divided into high-caloric expenditure exercise and low calorie expenditure exercise. The study was conducted for 12 weeks, and included 95 subjects aged 18 to 70, 46 belonging to the group of low caloric expenditure (46.1 years) and 49 to the group of high caloric expenditure ( $49.2 \pm 9.1$  years). After intervention, no difference was detected in serum BDNF levels in relation to pre-test, where the concentration remained stable. Also, there was no difference between the two groups in plasma BDNF. These findings do not corroborate those of Zoladz et al. [120], showing that even the long-term study was not able to promote positive changes in plasma concentration of BDNF. Something that should be highlighted is that the authors did not describe the adopted protocol of exercises (i.e., mode, intensity and duration), only mentioning it was high versus low calorie expenditure. Importantly, the sample was composed mostly of obese women. Thus, the results cannot be generalized to depressed thin male patients, for example. In addition, pre-treatment

**Table 1. Studies about interaction among BDNF, cortisol and acute aerobic exercise to predict neurobiological functioning in depression.**

Author/Year	Marker Assessed	Patients (n)	Mean age	Training	Medication	Number of Sessions	Session Duration	Days	Session Intensity	Supervised	Diagnostic Criteria	Instruments	Level of Depression	Randomized	Type of Treatment	Results
Krogh <i>et al.</i> [109]	Cortisol	44 CG 137 EG	38	Incremental test on cycloergometer	Yes	1	Up to exhaustion	1	Up to exhaustion	Yes	MDI	HRSD HARS	Mild to moderate	Yes	EPT	There were differences in the response of cortisol and GH between depressive patients and controls
Garcia <i>et al.</i> [110]	Cortisol	20 CG 23 EG	43	Incremental test on cycloergometer	-	1	Up to exhaustion	1	Up to exhaustion	Yes	DSM-IV	MADRS	Mild to moderate	Yes	ME	Exercise induced plasma cortisol secretion in patients with moderate depression
Wied <i>et al.</i> [111]	Cortisol	13 CG 23 EG	17 16	10 minute of cycloergometer (CG)	Yes	1	10 minutes	1	-	Yes	DSM-III	SCL-90 STAI (I)	Moderate to severe	No	Dexamethasone and hydrocortisone	Physical exercise increased cortisol output significantly in all subjects; no differences between groups
Käive <i>et al.</i> [112]	Cortisol	22 CG 24 EG	43	Incremental test on cycloergometer	Yes	1	Up to exhaustion	1	Up to exhaustion	Yes	DSM-IV	MADRS MMSE	-	No	ME	There were no differences in cortisol response between groups
Gustafsson <i>et al.</i> [113]	BDNF	18 CG 18 EG	33 34	Incremental test on a cycloergometer	No	1	Up to exhaustion	1	Up to exhaustion	Yes	DSM-IV	MADRS	Moderate	No	ME Dexamethasone suppression test	Increase in plasma BDNF depressive group 60 Minutes after exercise
Laske <i>et al.</i> [114]	BDNF	20 CG 35 EG	59 61	Incremental test on a treadmill	Yes	1	Up to exhaustion	1	Yes	Yes	DSM-IV	HRSD	Moderate to Severe	No	EPT	Significant increase of BDNF serum levels in MD patients after an exercise period
Ida <i>et al.</i> [21]	Cortisol	18		cycloergometer (EG) sitting quietly (CG)	Yes	1	15 minutes	1	11 to 13 in Borg (6 to 20)	Yes	DSM-IV	HRSD SF 36	Severe	No	EPT	The level of free cortisol saliva and subjective depressive symptoms decreased significantly after the exercise session.

ME = Monotherapy with Exercise - EPT = Exercise and Pharmacological Treatment - EG = Experimental Group - CG = Control Group - DSM = Diagnostic and Statistical Manual of Mental Disorders - CES-D = Center for Epidemiologic Studies Depression Scale - HRSD = Hamilton Rating Scale for Depression - HARS = Hamilton Rating Scale for Anxiety - TF = Pharmacotherapy - HK = High kilocalories - LK = Low Kilocalories - MMSE = Mini Mental of State Examination - MADRS = Montgomery Asberg Depression Rating Scale - HR = Heart Rate - HRR = Heart Rate Reserve - ET = Electroconvulsive Therapy - AE = Aerobic Exercise - RM = Repetition Maximum - HRmax = Maximum Heart Rate - Borg = Scale Perceived Exertion - VO<sub>2</sub>max = Maximum Oxygen Uptake - IDS = Inventory of Depression Symptomatology - MDI = Medical Depression Inventory (MDI) - STAI = State Anxiety Inventory - SCL-90 = The 90-item Symptom Checklist - SF-36 = Short-Form 36-Item Health Survey

**Table 2. Studies about interaction among BDNF, cortisol and chronic aerobic exercise to predict neurobiological functioning in depression.**

Author/Year	Marker Assessed	Patients (n)	Mean Age	Training	Medication	Duration (Weeks)	Session Duration	Days Per Week	Session Intensity	Supervised	Diagnostic Criteria	Instruments	Level of Depression	Randomized	Type of Treatment	Results
Krogh <i>et al.</i> [109]	Cortisol	42 Strength 47 Aerobic 48 Relaxation	38	Strength  Aerobic  Relaxation	Yes	16	60 min  20 to 30 min	2	50 to 75% 1RM  70 to 90% HRmax  max 120; Borg 12)	Yes	ICD 10 MDI	HRSD HARS BDI	Mild to moderate	Yes	EPT	There were no differences between groups in basal hormone concentrations
Nabkasorn <i>et al.</i> [32]	Cortisol	49	18	Recreational activities versus unsupervised run (cross over)	No	16	50 Min	5	50% of HRR	No	CES-D	-	Mild to moderate	Yes	ME	Physical exercise reduced depressive state and urine cortisol
Salehi <i>et al.</i> [116]	BDNF	60	30	Cycling on a treadmill	Yes	4	-	-	Between 60 and 75% of VO <sub>2</sub> max.	Yes	DSM-IV	HRSD BDI	Severe	Yes	ET AE ET + AE	Both treatments increased plasma BDNF levels and reduced depressive symptoms
Schuch <i>et al.</i> [117]	BDNF	15 EG 11 GC	-	Transport Cycloergometer or treadmill	Yes	3	-	3	59% HRR (16.5kcal/kg/week)	Yes	DSM-IV	HRSD	Severe	Yes	AE/PT/ET	Showed no difference in plasma BDNF levels after combined treatment with aerobic exercise
Toups <i>et al.</i> [115]	BDNF	46 LK 49 HK	38 32	-	Yes	12	-	-	-	Yes	IDS	HRSD	Moderate	Yes	ME PT	Resting serum BDNF was stable and did not correlate with energy expenditure

ME = Monotherapy with Exercise - EPT = Exercise and Pharmacological Treatment - EG = Experimental Group - CG = Control Group - DSM-IV = Diagnostic and Statistical Manual of Mental Disorders - CES-D = Center for Epidemiologic Studies Depression Scale - HRSD = Hamilton Rating Scale for Depression - HARS = Haminton Rating Scale for Anxiety - PT = Pharmacotherapy - HK = High Kilocalories - LK = Low Kilocalories - MMSE = Mini Mental of State Examination - MADRS = Montgomery Asberg Depression Rating Scale - HR = Heart Rate - HRR = Heart Rate Reserve - ET = Electroconvulsive therapy - AE = Aerobic Exercise - RM = Repetition Maximum; HRmax = Maximum Heart Rate - Borg = Scale Perceived Exertion - VO<sub>2</sub>max. = Cardiopulmonary Maximum Capacity - IDS = Inventory of Depression Symptomatology.

with SSRI (selective serotonin reuptake inhibitors) may have masked the effect of exercise on BDNF. It is also noteworthy that the study lacked a control group. The practice of different protocols (i.e., different duration and intensities) is needed to clarify this issue. Salehi *et al.* [116] carried out a randomized study and showed that 4 weeks of electroconvulsive therapy, aerobic exercise and both were able to increase serum BDNF levels and reduce depressive symptoms in 60 depressed patients. However, patients were treated with a SSRI antidepressant (i.e., citalopram). Therefore, one cannot determine whether the individuals had improvements in depressive symptoms and an increase in the plasma levels of BDNF due to electroconvulsive therapy and aerobic exercise. It is also noteworthy that this study lacked a control group too, and then it would be interesting to carry out a controlled study, with use of citalopram and without exercise practice. Moreover, the sample was mostly constituted by young males individuals (n = 41) with severe depression, and thus, these results cannot be extrapolated for an elderly population of depressed women, for example. Furthermore, the time interval between pre- and post-assessment has been established in four weeks, and there was no further evaluation or follow-up, which would have been enlightening to observe long-term changes in plasmatic BDNF and psychopathology. It is still unclear to what extent the peripheral BDNF effectively reflects BDNF availability in the CNS. Also, due to the importance of the HPA axis in depression, studies are needed to examine the activity of the HPA axis and its interaction with plasmatic BDNF. Schuch *et al.* [117] showed no difference in plasma BDNF levels after treatment associated with aerobic exercise of moderate to vigorous intensity. All patients (15 exercise and 11 control) received concurrently other therapies such as pharmacotherapy and electroconvulsive therapy (ECT). As shown in the study of Salehi *et al.* [116], ECT alone is already

able to increase levels of BDNF in depressed patients. Mata et al. [36] have shown that some genotypes can moderate BDNF responses to exercise. Furthermore, the study lasted only three weeks, which cannot lead to significant changes in the levels of BDNF. Thus, further studies with large sample, long-term duration and no drugs are necessary. It would also be interesting to compare different aerobic exercise intensities, so that there is a consensus on the true role of this type of exercise on BDNF levels of depressed individuals. This discrepancy may be due to the use of different samples and different exercise protocols. Toups et al. [115] performed a study on a chronic basis. Gustafsson et al. [113] and Laske et al. [114] applied the incremental test. Even so, the ergometers used were different. Gustafsson et al. [113] used the cycloergometer and Laske et al. [114] used the treadmill. The fact that there are few studies, and these few have used different exercise protocols and heterogeneous samples, does not allow us to draw a relationship between aerobic exercise and BDNF. Therefore, it becomes necessary to perform more studies with other groups of depressed patients, so it can be clarified the relationship between BDNF and aerobic exercise (for review, see Tables 1 and 2).

## NEUROBIOLOGICAL MECHANISMS

The neurobiological effects of exercise acting as an agent that can modulate mood appears to influence several neural mechanisms that are related to depression [16, 121]. There is evidence that the practice of exercise causes physiological changes in monoamine levels in rats [122], as well as in healthy men and women [123], alters the levels of cortisol in rats and healthy individuals [123-126] and leads to adaptations in limbic structures that have been implicated in depression, in addition to increased expression of neurotrophic factors in hippocampus of rats and healthy subjects [121, 125-131]. However, no evidence was obtained in depressed patients. A dysfunction in the serotonin (5-Hydroxytryptamin; 5HT) has been identified as the immediate cause of depression [132, 133]. A decrease in the levels of 5- hydroxyindoleacetic (5HIAA), the major metabolite of 5-HT on the human body, a decrease in plasma tryptophan acid, as well as low proportion of amino acid tryptophan and 5HT function abnormalities are commonly reported in studies of depression [134, 135]. It is noteworthy that the increase in monoamine levels can be achieved by the practice of chronic exercise. For example, significant levels of noradrenaline and 5HT and 5HIAA and the expression of 5-HT<sub>2C</sub> receptors in the limbic system have been reported in experimental animals following chronic exercise treadmill [122, 125, 136, 137]. While the activation of the HPA axis can be considered an adaptive mechanism based on the response to change, a high, prolonged activation of this system represents a health risk. Chronic stress is linked to hyperactivity of the HPA axis and elevated levels of glucocorticoids [138, 139]. Most groups of depressive patients display alterations in the HPA system, resulting in altered regulation of ACTH and secretory activity of cortisol [19, 140]. Rubin et al. [141] observed high levels of ACTH and cortisol secretion in depressed patients. Exercise, like other stressors, activates the sympathetic nervous system, resulting in the secretion of glucocorticoids [142, 143]. However, physically active people show different cortisol responses to acute exercise compared to less active individuals. Cortisol levels in physically active individuals is attenuated and dissipates more rapidly than in less active individuals [123, 124, 144]. Therefore, exercise can reduce symptoms of depression by its influence on the HPA system, attenuating the glucocorticoid response to stressful stimuli. Depression can lead to neuronal cell loss and atrophy in limbic regions of the brain, including the amygdala, and prefrontal cortex and hippocampus [11]. Depression is related to a decline in cognitive function in which the hippocampus plays a crucial role. Hippocampal neurogenesis has been associated with

improvements in learning and memory function [145, 146]. The hippocampus is also involved in regulation of the HPA axis in response to stress the system. Damage or atrophy of the hippocampus impairs this system, leading to a prolonged activation of the HPA axis in response to psychological stressors [147, 148]. High levels of glucocorticoid induce atrophic changes in sub-regions of the hippocampus [147], which is consistent with the reduction in volume of the hippocampus seen during depression. Patients with depression have shown smaller hippocampal volume than non-depressed controls [149]. The left hemisphere showed a significant reduction in the volume of the hippocampus in 19% of depressed patients compared with healthy controls. These results suggest that depression causes a loss of brain volume observed in the hippocampus, especially in the left hemisphere. As mentioned earlier [142, 143], the exercise, as well as other stressors, activates the sympathetic nervous system, resulting in the secretion of glucocorticoids. It has been shown that stress can reduce the expression of several neurotrophic growth factors in the hippocampus, while chronic antidepressant treatment acts on the opposite way [5]. Among the protective effects of exercise stress, we can highlight neurogenesis [129, 150] and the expression of the growth factor in the hippocampus [13]. Different stressful stimuli, such as acute immobilization stress [151] or administration of corticosterone [152], reduce the expression of neurotrophic factors in the hippocampus. Human studies have shown that the availability of BDNF deficiency is associated with vulnerability to depression [153]. Exercise training therefore compensates the atrophic changes of the hippocampus for its impact on the expression of neurotrophic growth factors, which have an antidepressant action similar to that hypothesized for the treatment of antidepressant drugs [127, 130, 154-157]. Thus, there is support for the neurotrophic hypothesis of depression as an alternative to any other hypothesis. In summary, these neurobiological results tend towards that the health of the brain depends from exercise, and that the regular practice should be promoted as prevention and rehabilitation strategy to prevent or treat brain related diseases.

## CONCLUSION

In this review on the effect of aerobic exercise on serum BDNF and cortisol in patients with depression, 11 studies were incorporated, aggregating a total of 508 individuals with MD, and 137 healthy controls. Of these eleven studies, six evaluated the relationship between exercise and cortisol, and five examined the relationship between exercise and BDNF. In general, no relationship was established on the impact that exercise has on the concentration of these two biomarkers. This may be explained by the difference across variables such as: type of exercise adopted; duration of the session; prescribed intensity and frequency of weekly sessions. It seems that just an exercise session is not able to influence in positive adaptations in cortisol levels and BDNF. Mistakenly, most of the papers, a total of five, adopted the cardiopulmonary effort test as aerobic exercise. However, it is noteworthy that the cardiopulmonary exercise test is, in most cases, an anaerobic activity, due to its intensity, which is submaximal or maximal, thus exceeding the anaerobic threshold of these individuals. Furthermore, only two studies have examined the chronic effects of physical exercise in concentration of cortisol, and one study adopted chronic exercise to investigate its role on plasma concentrations of BDNF. Thus, it would be interesting to conduct further studies on aerobic exercises in a chronic way, to establish a genuine cause and effect relationship between regular exercise and the investigated biomarkers.

## LIST OF ABBREVIATIONS

5-HT<sub>2C</sub> = 5-Hydroxytryptamin (Serotonin) Receptor 2C

5HIAA = Hydroxyindoleacetic Acid

5HT = 5-Hydroxytryptamin

ACSM = American College of Sports Medicine

ACTH = Adrenocorticotropin

BDNF = Brain Derived Neurotrophic Factor

CNS = Central Nervous System HPA = Hypothalamic-Pituitary-Adrenal Axis MD = Major Depression SSRI = Selective Serotonin Reuptake Inhibitor

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