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Trace elements and physical activity in children and adolescents with depression

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Abstract: Depression is a common mental health problem among adolescents. Depressive symptoms are also important and may appear even during the preschool period. Physical activity, which may improve some mental health problems, is inversely associated with depression. Due to the presence of some clinical evidence about the relation between the use of antidepressants and suicide, there is a need for supportive agents during antidepressant therapy. Within this context, essential trace elements gain importance for further consideration. Protection of the developing brain from the negative effects of iron deficiency is important because of iron deficiency's association with poor mental development. Reactions between copper and serotonin may contribute to the development of depression because copper may cause alterations in dopamine and norepinephrine levels. Some links between zinc deficiency and depression-like behavior have been noted. The antidepressant-like activity of zinc involves interaction with the serotonergic system. Selenium supplementation significantly improves individuals' mood scores. Low selenium status is associated with depression and anemia, which may lead to poor mental development. The influence of physical activity on trace elements should also be considered. The possible associations between members of neurotransmitter systems and metals as well as physical activity are reviewed here in relation to depression in the youth population. Elevated or reduced levels of metals may be indicators of depression. Intervention toward normalization of the profile of essential trace elements may prevent the development of depression and support the effects of therapy in depressive individuals.

Key words: Child, adolescent, trace element, metal, depression, physical activity

Çocuklarda ve genç erişkinlerde görülen depresyonda eser elementler ve fiziksel aktivite

Özet: Depresyon genç erişkinler arasında yaygın görülen bir akıl sağlığı problemidir. Depresyon belirtileri okul öncesi dönemde bile ortaya çıkabilir. Bazı akıl sağlığı problemleri üzerinde olumlu etkisi gözlenen fiziksel aktivite depresyon ile ters ilişkilidir. Antidepressan kullanımı ve intihar arasındaki ilişki ile ilgili bazı klinik delillere bağlı olarak, antidepressan tedavi sırasında destekleyici ajanlara gereksinim duyulmaktadır. Bu bağlamda, esansiyel eser elementler ileriye yönelik araştırmalar için önem kazanmaktadır. Gelişmekte olan beyinin, yetersiz zekâ gelişimi ile olan ilişkisi nedeniyle demir eksikliğinin olumsuz etkilerinden korunması, demir düzeyinin önemine işaret etmektedir. Bakır, dopamin ve norepinefrin düzeylerinde değişikliklere neden olabildiğinden, bakır ve serotonin arasındaki reaksiyonlar depresyonun gelişmesine katkıda bulunabilir. Çinko eksikliği ile depresyon benzeri davranışlar arasında bazı bağlantılar bildirilmiştir. Çinkonun antidepresan benzeri aktivitesi serotonerjik sistem ile olan etkileşimi içermektedir. Selenyum desteği, bireylerin ruhsal durumlarını önemli ölçüde iyileştirmektedir. Düşük selenyum düzeyi, depresyon ve yetersiz zihinsel gelişmeye yol açabilen anemi ile birliktelik göstermektedir. Fiziksel aktivitenin eser elementler üzerine olan etkisi de göz önüne alınması gereken bir husustur. Bu makalede, fiziksel aktivite ile metaller ve nörotransmitter sistemlere ilişkin parametreler arasındaki olası ilişkiler, çocuk ve gençlerde görülen depresyonla bağlantılı biçimde gözden geçirilmiştir. Artmış ya da azalmış metal düzeyleri depresyon göstergeleri olabilirler. Esansiyel eser element profilinin normalleştirilmesine yönelik girişimler, depresyonun gelişmesini önleyebilir ve depresyonlu bireylerde tedavinin etkisini destekleyebilir.

Anahtar sözcükler: Çocuk, genç erişkin, eser element, metal, depresyon, fiziksel aktivite

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Introduction

Depression is a disease that frequently occurs in childhood and adolescence. Depression is present in about 1% of children and 5% of adolescents. Suicidal behavior, which is a common cause of death, especially in young people, is closely associated with depression (1-3).

Biological markers of serotonin (5-hydroxytryptamine, 5-HT) are decreased in depression. Pharmacotherapy is based on the enhancement of serotonergic and/or noradrenergic neurotransmission, either by inhibiting the degradation of monoamines by monoamine oxidase (MAO) inhibitors or by blocking their uptake back into the synaptic cleft by selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCA) (4,5). SSRIs and SNRIs bind the monoamine transporter proteins with high selectivity and affinity, block the neurotransmitter translocation process, and lead to an increase in synaptic monoamines (6,7).

It is generally accepted that physical activity (PA) is associated with children's mental health as well as their physical and psychological well-being (8,9). Exercise was also found to be associated with prevention of depressive disorders (8-14).

Considering that essential metals are multi-faceted with their beneficial (15) and harmful (16) properties, it is reasonable to suggest that they may also influence the neurotransmitter systems. In this article, the possible associations between the members of this system and metals as well as PA are reviewed in relation to depression in the youth population.

Child and Adolescent Depression

Depression continues to be the most common mental health problem among adolescents and requires psychological support (17). Depression can also arise during the preschool period. Recent reports have pointed out depression before the age of 6, and the symptoms may arise as early as age 3 due to shame and guilt (18,19). Early life stress predisposes individuals to the development of subsequent psychiatric illness, including major depressive disorder. Lower brain 5-HT transporter binding potentials (5-HTT BP_p) in depressed subjects have recently been shown to be associated with reported histories of childhood abuse (20). Depressive symptoms in children may appear in conjunction with problematic mother-child interactions. For example, pain, which may be associated with depressive symptoms, as well as some alterations in metal and neurotransmitter metabolisms in children and adolescents with headaches, may cause parent-adolescent conflict (21,22). In a similar manner, maternal depression is associated with toddler behavioral problems, which may persist into late childhood (23). Maternal depression is also a risk factor for depressive and anxiety symptoms, which increase in frequency over the first 5 years of life.

Effects of Physical Activity on Mental Health and Depression among Children and Adolescents

Effects of Physical Activity on Mental Well-Being

The number of studies that find PA beneficial for child and adolescent mental health status is increasing (8,9,11,24-28). The literature on the relation between PA and children's health requires future investigation. PA may be a critical factor affecting children's immediate and long-term health. The need to promote exercise and lifestyle, including PA, is introduced as a means of enhancing children's positive well-being (29). Significant associations between exercise and positive mood were observed (30). Significant increases in positive emotions and decreases in negative emotions prior to and after exercise and higher levels of pride with natural (outdoors in a natural environment) rather than laboratory (indoors on a laboratory treadmill) running for 5 km were detected (31). Children who met recommended levels for PA had fewer emotional problems 1 year later (32). Weekly hours of PA at the ages of 15-16 years influenced mental health positively 3 years later in boys (33). Physical activity for children is also important for promoting good sleep (34). The impact of sleep on mental health during adolescence has been investigated and adolescent sleep chronobiology was found to be associated with psychological well-being (35).

Effects of Physical Activity on Depression

PA may have physiologic effects on depression due to an increased release of β-endorphins and brain neurotransmitters such as 5-HT, dopamine (DA), and

norepinephrine (NE) (36). Fitness training was associated with positive emotional and behavioral responses, in addition to reduction of depressive symptoms (14). A 9-week exercise intervention plan (20-30 min, 3 days per week) caused a reduction in the symptoms of depression (13). Adolescents who engaged in regular PA were characterized by lower anxiety-depression scores and displayed less social and behavioral inhibition than their less active counterparts (8). PA time was inversely associated with depression in adolescents (11,24,37). Compared to the inactive group (0-0.9 h of PA time per week), active students who spent at least 1 h per week on PA were at significantly lower (<30%) risk of being depressive, and their odds of being depressive decreased from 63% to 58% and 53% as PA time increased from 1-7 h/week, 8-14 h/week, and 15+ h/week, respectively (37). For example, in children assigned to an aerobic intensity PA program, significantly less depression was reported (25). Similarly, a beneficial effect of PA on feelings of sadness and suicidal behaviors was observed (26).

In another study, exercise diminished the clinical symptoms of patients with psychiatric disorders. Especially in the case of patients with depression, endurance exercise significantly improved their mood (27). Upon examination of the relation between depression and PA, a significant reduction in depression was found among preadolescents enrolled in after-school exercise programs. Findings supported social, cognitive, and self-efficacy theories as well as the association between PA and improved mental health in preadolescents (28).

The relation between PA and child/adolescent mental health status is improving. Involvement of oxygen with respect to oxidative stress, particularly in aerobic exercises and its association with metals, makes the topic more complicated. Evaluation of the topic as a whole will lead to a solution for the problem.

Life Course from Depression to Suicide

The Relation between Depression and Suicide

Psychotic disorders and psychotic-like experiences may increase the risk of suicidal problems among adolescents (38,39). Major depressive disorder causes significant morbidity, affecting people's ability to work, function in relationships, and engage in social activities, and also increases the risk of suicidal ideation, attempted suicide, and death by completed suicide (40).

Long durations of depression (>13 months), anhedonia, feelings of worthlessness, comorbid anxiety, previous suicidal ideation, and the use of professional care are important determinants of suicidality among depressed patients (39,41). Repetition of suicidal behavior is associated with high anxiety, severe depression, and other psychiatric symptoms, and is increased in young patients (42).

Suicide is among the 3 leading causes of death for adolescents in the world, and suicide rates are rising faster among teenagers than for other age groups. Since depression can lead to many adverse results, including academic dysfunction, increased arguments with family members, and suicide, a major issue in suicide prevention is the screening of all children and adolescents for depression and other factors that may trigger suicide in adolescence (43).

Considerations and Possible Risks Regarding the Use of Antidepressant Medications in Children and Adolescents

Maternal depression increases the risk of emotional and behavioral problems in children (44). Adolescent depression is also a serious illness associated with substantial morbidity and mortality (1). SSRIs are the most commonly used treatment for adolescent depression (2).

Today the safety of the newer antidepressant drugs, including SSRIs, is still under review. The important question is whether SSRIs increase the risk of suicidal behavior in depressed children (1). Many antidepressants are excreted in breast milk (45,46). No psychotropic drug is free of potential negative effects. Fluoxetine is the only SSRI currently approved for pediatric use; however, some cautionary remarks have been made about it (45).

Effects of treatment among children and adolescents need to be understood better, because data indicate that age is a modifier of treatment effects (47). Treatment with SSRIs does not increase the risk of suicide in adults; however, in children, adolescents, and young adults being treated with antidepressants, there is a tendency of a rise in the risk of attempted suicide (48,49).

Clinical Evidence on Antidepressant-Induced Suicidality

Suicidal thoughts and suicide attempts have been higher among depressed children and adolescents receiving antidepressants than among those receiving placebos in controlled clinical trials (45). These documented links between the use of antidepressants and suicide are very important. The Federal Drug Administration's meta-analysis suggests that "Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers and young adults when the medicine is first started" (50,51). Findings of a relation between suicidality and completed suicide point out the possibility of an increased risk of suicidality due to antidepressant drugs and the limited knowledge about antidepressants, particularly in terms of their pediatric use (52).

The relation between exposure to SSRIs and the risk of suicide is influenced by age. Among adolescents, use of antidepressants is associated with a significantly increased risk of suicidal adverse events (53,54). Suicidal ingestions of SSRIs, SNRIs, and other antidepressants peaked in teens (55). The risk of suicidal thoughts and behaviors in the treatment of depressive children and adolescents with SSRIs and SNRIs is slightly but significantly elevated (56). In another study, an overall increased risk of suicidal ideation was reported during pediatric antidepressant treatment, as compared with placebo treatment (57). There are also studies reporting that treatment of depressed youth with antidepressants, including SSRIs, carries a small increased risk of suicidality (47,58). Antidepressants should be used cautiously in adolescents who are under the threat of increased risk for suicide (54,59).

Present Situation of Psychopharmacotherapeutic Interventions for Suicidal Behaviors

Children appear to be at a higher risk than adults for drug-induced adverse effects. Both the needs of children being treated and the seriousness of the adverse effects call for large-scale clinical studies to understand the mechanisms underlying toxicities and to develop effective preventive and treatment strategies (60). Upon analysis of the Treatment for Adolescents with Depression Study (TADS) database, the severity of self-rated suicidal ideation and depressive symptoms predicted the emergence of suicidality during treatment. Depressed adolescents who manifest suicidal ideation at the beginning of the treatment are at increased risk of suicidal events during treatment. The risk of suicidal events does not decrease after the first month of treatment, suggesting the need for maintenance of careful clinical monitoring during treatment (61). The clinical trials on adolescent depression provide information on the benefits and limitations of current treatments (62).

Nutritional Aspects

Since there are great controversies related to the usage of antidepressant medications in children and adolescents, it is reasonable to search for remedies that may be associated with some related parameters. Nutrition gains importance when depression is considered. Dietary metals are closely involved with behavior and cognition. The controversial effects of phytochemicals as well as toxic metals should also be considered (63-66). Due to the close relationship between depressive disorders and suicidality, and the possible effects of dietary metals on people's behavior and cognition, a discussion about trace metals and depression would be helpful.

Trace Elements-Induced Changes Affecting Neurotransmitter System Parameters

The metals deserve attention in the field of neurotransmitters and related metabolisms. It is worthwhile to investigate the association between metals and depression because elements play vital roles in human metabolism (67). A vast amount of information in the scientific literature on trace elements aims to establish some important medical and diagnostic links between the metal concentrations and various diseases. Therefore, the possible relations among trace elements, physical activity, and neurotransmitters in the depression of children and adolescents are reviewed.

Iron

Iron (Fe) needs to be administered to augment physical capacity during exercise; however, during athletic activity, Fe may damage tissues by catalyzing the conversion of hydrogen peroxide to free radical ions. Both Fe deficiency and excess are deleterious (68).

Fe, an essential metal indispensable for human health in trace amounts, is extremely dangerous and harmful in excess amounts. Free Fe can cause considerable oxidative damage through the Fenton reaction. Tryptophan, an essential amino acid serving as the precursor for serotonin, has the special ability to bind Fe. Tryptophan can form some carcinogenic metabolites that are only toxic when combined with Fe (69). Fe may induce cancer through oxidative damage and the formation of complexes with tryptophan. Fe, by reacting with tryptophan, can reduce the production of serotonin and melatonin (70,71), parameters associated with depression.

The Fe status of the mother determines the child's Fe status. Iron deficiency (ID) during late fetal and early neonatal life is a risk to the developing brain, manifesting with alterations in brain function during the newborn period. It is important to protect the developing brain from the negative effects of ID during infancy because of ID's association with poor mental development (72-74). An association between depression and decreased ferritin levels detected among medical students may point to low Fe status as an indicator of depression (75). Fe deficiency is an important health problem in children, women of child-bearing age, and pregnant women, in both developed and developing countries. Fe excess also threatens the health of young individuals. Therefore, interactions of Fe with many essential and toxic metals are worth mentioning.

Copper

Some members of antioxidative systems (Cu/Zn-SOD, Cu-thioneine) and enzymes such as tyrosinase, tyrosine hydroxylase, and dopamine-β-hydroxylase require copper (Cu) for their optimum activities. Therefore, copper deficiency may lead to reduced catecholamine synthesis.

When present in high concentrations, Cu can cause some problems in the brain. It can impair zinc (Zn) uptake. Free radicals are associated with low Cu/Zn-SOD activity. Therefore, Cu, which favors free radical formation reactions in its excess amount, can devastate the brain. Copper, being the cofactor for tyrosinase, causes increased synthesis of DA, which inhibits the tryptophan hydroxylase required for 5-HT synthesis (70,71).

Serotonin, an important neurotransmitter in the brain and spinal cord, is involved in the control of sleep, consciousness, aggression, and mood. It is also implicated in disturbances such as anxiety and depression. In the presence of Cu, serotonin is capable of causing strand cleavage in DNA and cell death through an oxidative mechanism. Serotonin reduces Cu^{2+} to Cu^{1+}. The latter participates in the generation of hydroxyl radicals. Serotonin is able to bind DNA and Cu ions. Since Cu is an essential component of chromatin, the formation of a serotonin-Cu-DNA complex is possible (76,77).

Copper is involved in some physiological systems, such as conversion of DA to NE, signal transduction, intracellular calcium mobilization, and energy production via cytochrome c oxidase, which participate in the development of postpartum depression (PPD). There may be an association between elevated Cu levels and PPD. Elevated Cu levels may cause alterations in DA and NE levels in women with PPD. PPD, which occurs during the post-natal period, may be associated with suicidal and homicidal behavior in severe cases. Depression in mothers increases the risk of emotional and behavioral problems in children. Maternal depression and adjustment problems of the child are common health problems and impose significant burdens on society (44,78).

Cu homeostasis is essential during PA and sports (79). During intense physical exercise, superoxide dismutase (SOD) activity is increased, favoring the adaptation of Cu metal (80-82). Since Cu is a double-edged sword, the delicate balance between its deficiency and excess states is extremely critical; its concentration must be evaluated carefully so that a deficiency is corrected by supplementation or an excess is removed through chelation. The contradictory results reported in athletes complicate the interpretation of the effect of PA on depression from the point of view of Cu.

Zinc

Zn is essential for physical growth and development. Fetal neurobehavioral development improves during pregnancy when Zn is added to Fe and folate supplements (74).

Zn acts as a neuromodulator at excitatory synapses and plays a role in the stress response and in the functionality of Zn-dependent enzymes, contributing to the brain's compensatory capacity. The mechanisms that modulate the free Zn pool are pivotal for brain health and performance (83). Zinc can cause deficiencies or imbalances of other metals. Absorption of Fe and Cu from the intestine is limited by Zn (74).

Many contradictory results were observed about the association between Zn and PA. Zn as a component of SOD protects against the formation of reactive oxygen species (ROS). Athletes of long-distance, high-impact aerobic modalities had higher indices of antioxidant protection, e.g., erythrocyte Zn, SOD, and metallothionein, than those of short-distance, low-impact modalities. This suggests the adaptation of the antioxidative defensive mechanisms to PA and indicates that an adequate Zn status is important for the effectiveness of antioxidant mechanisms in response to intense exercise (68,81,84).

Severe Zn deficiency in pregnancy adversely affects mental development and behavior. Zn may regulate 5-HT and NE content in the brain by inhibiting MAO-A activity. A link between Zn deficiency and mood disorders such as depression-like behavior has been pointed out (85-87). A relationship between depression and low Zn was noted in cases of PPD (88).

Although an insignificant relation between Zn status and depression was reported among thalassemia patients in a single study (89), Zn plays a significant role in the improvement of depression (90). Zn may be a sensitive and specific marker of depression because Zn exhibits antidepressant-like activity in models of depression, and also has an effect on the N-methyl-D-aspartate (NMDA)/glutamate pathway in suicide victims (91). The antidepressant-like activity of Zn observed in the forced swim test involves interaction with the serotonergic system (92) and is correlated with an alteration in the function of the NMDA receptor (93). Zn supplementation enhances the efficacy of pharmacotherapy in affective disorders because of its potential clinical antidepressant activity (94,95). Zn is involved in the regulation of brain-derived neurotrophic factor expression, which plays a key role in the pathophysiology and treatment of depression (96). Recent reports on Zn augmentation therapy have introduced the potential use of Zn in combination with pharmacologic treatment for the strongest effect in treating mental health problems (97,98). These findings suggest the use of Zn as a potential antidepressant agent.

Zn supplementation is required in the areas where Zn deficiency is common. However, *Helicobacter pylori* (HP), prevalent in developing countries and the cause of gastric cancer as well as HP infection, requires Zn for growth and virulence. Aflatoxin (AF), a common food contaminant, causes impaired growth and immune system disorders in such areas. Zn is also needed for the enhancement of *Aspergillus flavus* biomass and AF production. These factors should also be considered during interventions related to Zn supplementation performed for the improvement of mental health status in children.

Selenium

Selenium (Se), another essential element, possesses antioxidant functions as an integral component of glutathione peroxidase (GSH-Px). Selenoproteins protect neurons. Low Se status is associated with depression. Se toxicity is also important. Increased exposure to Se causes nervous system disorders in humans. Alterations related to DA metabolites caused by inorganic Se, which is more neurotoxic than organic Se, suggest a Se-specific increased neural activity of dopaminergic pathways (99-101).

Se is an important modulator of moods. Experimental studies reported that individuals fed with marginally low Se diets displayed more symptoms of depression than individuals fed with higher Se diets (102,103). As compared to the placebo, Se supplementation significantly improves individuals' mood scores (104).

Low Se status is associated with anemia (105), which may lead to poor mental development among school children. Alcohol consumption among adolescents may lead to a deficiency of micronutrients, including Se. The harmful effects of alcohol on mood, behavior, and cognition may be partly mediated by biological changes related to Se

deficiency. Preventive or therapeutic compounds that contain Se may be beneficial for psychiatric and neurological conditions (100,101).

During PA, oxidative stress due to excessive oxygen consumption is compensated by higher levels of free radical scavengers and by an increase in the activities of antioxidant enzymes (68,82,106-108). Few results are available concerning Se concentration during or following PA, and the levels of GSHPx reported in athletes are divergent (109,110). It is reported that athletes are generally not affected by Se deficiency. Therefore, Se supplementation should be carried out with particularly great care in athletes because of the 5-HT reducing effect of high Se.

Concluding remarks

The concept of trace elements covers a broad area and their spectrum is extremely wide. Toxic metal excess and/or essential metal deficiency-induced increases in MAO activity are noteworthy (85,86,111). Greater attention should be paid to nutritional factors in psychiatry. Consideration of the multiple aspects of trace element actions on the metabolisms of 5-HT, DA, and NE in combination with the current therapy protocols could offer a more effective treatment for depressed patients and suicidality. Trace elements, present in tiny amounts, occur at the crossroads of the metabolic pathways, including those of neurotransmitters. They are also closely related to radical formations, and thus to oxidative stress, which is known to be involved in the pathogenesis of many clinical disorders.

Besides nutrition, the parameters that may possibly be related to metal metabolism are quite important for mental health. Infections such as HP infection are also involved in this discussion. Aside from their association with increased ROS formation, one should also consider the relations between infectious agents and metals (112,113). If the facts that Zn is essential for the growth and virulence of HP and is also a stimulator of *Aspergillus flavus* growth and AF production are underestimated, then it may be difficult to achieve success in supplementation programs organized to overcome Zn deficiency, which are important in preventing mental health disorders such as depression and schizophrenia among young people. In trying to improve the mental health status of the population, an increase in high AF exposure or high HP prevalence may occur. This is particularly important for the pediatric population and pregnant women.

Elevated or reduced levels of metals may be indicators of depression. Interventions toward normalization of the profile of essential trace elements may prevent the development of depression and exert therapeutic effects in depressive individuals.

The evidence has demonstrated that within the scope of integrated metabolic pathways, SSRIs and SNRIs are not alone in the course of treatment. Consideration of metals along with oxidative stress markers may be suggested as a key to depression and its potential ultimate result, suicide, and will set the stage for a new era of more effective therapy to reduce mortality from suicide in depressed subjects.

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