The role of testosterone in clinical manifestation of mental disorders and type 2 diabetes: a literature review

Testosterono vaidmuo psichikos sutrikimų ir 2 tipo cukrinio diabeto klinikoje: literatūros apžvalga

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SUMMARY

Introduction. Testosterone is one of the major circulating androgens in the human body. Studies on testosterone have shown that testosterone plays an important role not only in pathogenesis of various somatic diseases, e.g. type 2 diabetes, but is also important of the development of mental disorders – anxiety, depression and neurodegenerative disorders. In this article we will review the effect of testosterone in manifestation and treatment of disorders, including mental disorders.

Aim. To review the experience of clinical trials and the most relevant study data between testosterone and the development of anxiety, depression, neurodegenerative disorders and type 2 diabetes and the role of testosterone therapy as an option to manage these disorders.

Methods. Literature search was performed using OWID (ourworldindata.org) statistics and research published in the PubMed database , that reviewed the role of testosterone in the development and management of mental, neurodegenerative disorders and type 2 diabetes.

Results. Augmentation of primary drugs with testosterone or testosterone replacement therapy could be used to treat anxiety, depression, neurodegenerative disorders or type 2 diabetes in some groups that meet narrow criteria, but the results of some studies remain controversial. To ensure safety of treatment augmentation with testosterone replacement therapy extensive long-term controlled clinical trials are still required.

Keywords: testosterone, anxiety, depression, type 2 diabetes, neurodegenerative disorders

SANTRAUKA

Ivadas. Testosteronas yra vienas iš pagrindinių androgenų, cirkuliuojančių žmogaus organizme. Atliekant tyrimus susijusius su testosteronu pastebėta šio hormono svarba ne tik įvairių somatinių ligų, tokių kaip 2 tipo cukrinis diabetas patogenezėje, bet ir psichikos sutrikimų – nerimo, depresijos, neurodegeneracinių ligų išsivystymui. Šiame straipsnyje apžvelgsime testosterono poveikį sutrikimų pasireiškimui bei gydymui, įskaitant ir psichikos sutrikimus.

Tikslas. Apžvelgti klinikinių tyrimų patirtis bei aktualiausius literatūros duomenis apie testosterono sąsajas su psichikos sutrikimų, tokių kaip nerimo, depresijos, neurodegeneracinių ligų bei 2 tipo cukrinio diabeto išsivystymui bei galimą testosterono vaidmenį šių ligų valdyme bei gydyme.

Metodai. Literatūros apžvalga buvo atlikta naudojantis OWID statistiniais duomenimis (ourworldindata.org) ir paieška PubMed duomenų bazėje pateiktais tyrimais bei apžvalginiais straipsniais apie testosterono vaidmenį psichikos sutrikimų, neurodegeneracinių ligų, 2 tipo cukrinio diabeto išsivystyme bei jų valdyme.

Rezultatai. Pagrindinio medikamentinio gydymo augmentacija testosteronu galėtų būti naudojama nerimo, depresijos, neurodegeneracinių ligų arba 2 tipo cukrinio diabeto gydyme, tačiau dalies tyrimų rezultatai išlieka kontraversiški. Tam, kad būtų saugu naudoti testosterono pakaitinę terapiją augmentuojant ligų gydymą, dėl didelės nepageidaujamo poveikio tikimybės yra reikalingi didesnių apimčių ilgalaikiai kontroliuojami klinikiniai tyrimai.

Raktiniai žodžiai: testosteronas, nerimas, depresija, 2 tipo cukrinis diabetas, neurodegeneracinės ligos

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INTRODUCTION

Testosterone, also known as a primary sex hormone, anabolic steroid in males or an androgen, by chemical structure is a 19-carbon steroidal derivative of cholesterol. First, cholesterol is converted to pregnenolone within mitochondria by the side-chain cleavage enzyme (P450scc). After that, by other P450 enzymes pregnenolone is converted to a different androgens [e.g., dehydroepiandrosterone (DHEA) and androstenedione]. In the human population the dominant circulating androgen is testosterone [1, 2]. Leydig cells of the testes produce 95% of circulating testosterone (6–7 mg/day) in mens body [3], compared to ovaries in the female body these cells produce 7 to 8 times higher testosterone [4]. A lot of studies were measuring the endogenous level of testosterone. They came to the conclusion that circulating testosterone levels affected amygdala activity among females and males [5, 6], which plays an important role in normal emotional response and psychiatric disorders.

In recent studies it was found that testosterone levels have significant effect on hormone sensitive cancers, type 2 diabetes (T2D), insulin resistance, body fat composition and other related metabolic disease risk factors. Ruth et al. (2020) study found causal positive effects of testosterone levels on lean body mass and number of lifetime sexual partners, which suggests testosterone effects on behavioral patterns [7]. Multiple studies have shown that levels of total and free testosterone is decreasing with age, but the extent of which decline in testosterone is caused by chronic illness, medication use or other factors isn't clearly distinguished from normal decline caused by normal aging [8, 9]. The symptoms of hypogonadism such as tiredness, lack of energy, reduced strength, frailty, loss of libido, decreased sexual performance depression, mood change and are not easily distinguished from symptoms of old age [10]. In this article, we will review the role of testosterone on the onset of type 2 diabetes and other conditions, including mental disorders.

METHODS

This literature review was performed using search criteria on keywords in Our World In Data (OWID) statistics database [11] and the PubMed database. Using keywords 293 articles were selected according to the search criteria. A search of literature on the causes, physiology, and treatment options for type 2 diabetes, depression, anxiety, neurodegenerative disorders including testosterone was carried out. Only English language and full text articles were included in this review. At the end 66 articles were used for this review.

RESULTS

The role of gonadal hormones in affective disorders

In 2017 there were 284 million people with anxiety disorders, making it the most prevalent psychiatric disorder. Around 63% (179 million) of patients with anxiety disorders were female, relative to 105 million males [12]. Current human research has yet to provide a clear understanding of the neural and behavioral mechanisms underlying their etiology, but different prevalence among gender suggests that gonadal hormones are playing an important role in etiology of anxiety and depressive disorders. It is known that the symptoms of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) occur during fluctuations of gonadal hormones, when estradiol (E2) and progesterone levels are low [13]. Women are more likely to suffer from anxiety during periods of gonadal hormone fluctuations including the premenstrual, postpartum and perimenopausal periods [14]. Data shows that incidence of mood disturbance and anxiety disorders increases as women progress toward menopause, corresponding to a period of falling E2 levels [15, 16]. Recent data shows that higher serum total testosterone and androstenedione in men may relate to an increased risk of anxiety disorders [17] and contradicts findings that testosterone and estradiol exhibit anxiolytic- and antidepressant-like effects in gonadectomized rats [18]. Hypogonadal men have much higher prevalence of anxiety disorders and major depressive disorder, compared to those with normal physiological levels of androgens [19]. Many studies found that testosterone appears to be effective in alleviating anxiety and/or depression in hypogonadal men, but risk factors must also be assessed [16, 20-22].

Major depressive disorder (MDD) is usually a chronic illness with women being two times more likely to be diagnosed with the disorder than man [23, 24]. There are differences in symptoms of MDD between men and women. Women usually have higher MDD related distress and higher severity of symptoms compared to men, also they are more likely to have hyperphagia, hypersomnia, a seasonal effect on mood and anxiety disorder along with their depression as comorbid disease [25, 26]. There is a lot of discussion between testosterone and depression, because testosterone is often described as a neuroactive steroid hormone, which carries weight for mood and appetitive behavior. A lot of studies have investigated the role of testosterone replacement therapy to reduce depressive symptoms and got good results [27, 28]. Giltay found that salivary testosterone levels are lower in female patients with a depressive disorder, generalized anxiety disorder, social phobia, and agoraphobia when compared to female controls but not in men [29]. Bromberger found that higher testosterone levels may contribute to higher depressive symptoms in women. In male patients with depression free testosterone index (FTI) was suggested as the most sensitive biomarker directly showing bioavailable testosterone level [30]. Milman found that higher levels of testosterone was strongly associated with depressive symptoms in Caucasian women [31]. Almeida et al., found that men with depression had significantly lower total and free testosterone concentrations than nondepressed men [32]. It was also observed that men with low testosterone levels more often have depressive symptoms [32, 33], but in some middle-aged and older men conflicting cohort studies there isn't any association between lover testosterone level and depression, only in solitary subtypes of depression. There is another side of testosterone. Some research has shown that the beginning of major depressive disorder in women can be caused by too much testosterone. Also in women excess testosterone can negatively impact their mood [34]. Recent population-based, longitudinal study revealed inverse associations between sex hormones and depressive symptoms and concluded that in general population, androgens and SHBG were not independently associated with depressive symptoms [35]. Since most of the trials that find associations between testosterone and depressive disorder are in very narrow populations or specific age groups, findings

are still contradictory, additional double blind, placebo-controlled, randomized clinical trials are warranted for decisive conclusions.

Gender differences in neurodegenerative disorders

Neurodegenerative disorders like Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS) are characterized by progressive changes of neuronal function in the brain and causes many psychiatric conditions, loss of cognitive and motor functions and the consequent death of patients [36]. There are significant gender differences in incidence of neurodegenerative disorders, twice as many men than women suffer from PD [37] and ALS is more common in men, and in younger age with differences in clinical features [38]. As well as being more likely to be diagnosed with AD, women have been reported as showing greater cognitive deficits than men even in verbal abilities [39]. Circulating levels of androgens and estrogens could have a role in determining gender differences in neurodegenerative diseases. With an increasing number of recent studies confirming testosterones neuroprotective properties [40-42] and although the role of testosterone in the central nervous system (CNS) is still poorly understood. It is important to consider testosterone as a treatment option for neurodegenerative disorders and even to monitor it as a tool for preventative measures. According to Moffat et al., which used a prospective, longitudinal design with follow-up in men since 1958, calculated free testosterone concentrations were lower before diagnosis in men who developed Alzheimer disease. So testosterone may be important for the prevention and treatment of AD [43]. It is important to take into consideration, that effect of testosterone vary depending on age group and levels of testosterone, which suggest that it is possible that there is an optimal levels of testosterone and Sex Hormone Binding Globulin (SHBG), which, if surpessed, is not beneficial but rather has negative effects on cognition [44-46]. Recent studies showed that testosterone administration does improve verbal memory, spatial memory in elderly men [47] overall cognitive functions in men with Alzheimer disease and mild cognitive impairment [48] and as a preventative measure against cognitive decline healthy older men [49].

The role of testosterone on insulin resistance in type 2 diabetes

Many studies show that hypogonadism is associated with insulin resistance in healthy men and can be used to predict T2D in middle aged men, and around one third of men with T2D have low levels of testosterone [50-54]. After studies of hypogonadism in men with T2D have highlighted that low testosterone is an independent risk factor for T2D and testosterone therapy might reduce insulin resistance. Many studies tried to investigate testosterone replacement therapy for hypogonadal men with T2D and investigate its effect on T2D outcomes [55]. Found beneficial effects on insulin resistance, total and LDL-cholesterol, sexual health and body composition in hypogonadal men with T2D [56]. Hackett found that testosterone therapy significantly improved metabolic parameters in men with T2D but only in groups with testosterone deficiency syndrome (TDS) and not in groups with severe TDS. In study by Ng Tang Fui et al., it was found that testosterone treatment significantly reduced the metabolically important visceral fat compared to placebo group [57]. Testosterone therapy also improved glycaemic control, insulin resistance, cholesterol and visceral adiposity and overall cardiovascular risk in hypogonadal men with T2D [58]. Long term studies also proved that testosterone therapy can help improve obesity, glycemic control, blood pressure, and HbA1c [59].

Testosterone as a treatment option in mental disorders

Treatment in patients with depression might require more than 1 treatment step, and more than 30% of patients do not experience sustained symptomatic remission even after 4 treatment steps, and poorer longer-term outcomes were found with participants who required more treatment steps [60], which is why it is important to look into more effective treatment options from first treatment steps. Placebo controlled trial with testosterone therapy in medically healthy adult men with MDD failed to show significant outcomes [61]. Zarrouf et al., found that testosterone showed antidepressant effect in men with hypogonadism or HIV/AIDS and in elderly subpopulations only [16]. Snyder et al., concluded that testosterone therapy showed some benefit with respect to mood and depressive symptoms in males, 65 years or older with low levels of testosterone [62]. Shores et al., confirms effectiveness of testosterone therapy for elderly men with low levels of testosterone for subthreshold depression or late-onset male dysthymia [63, 64]. Recent meta analysis and systematic review done by Walther [65] concludes that testosterone treatment appears to be effective in reducing depressive symptoms in men, particularly when higher-dosage regimens were applied in specific samples. Kleeblatt et al., found that testosterone was clinically effective for depressed hormone-deficient patients who are not responding to antidepressant monotherapy or established augmentation strategies [66]. Randomized study by Ditchel found no effects of testosterone therapy for women with antidepressant-resistant major depression, compared to placebo [67]. Budoff et al., found that testosterone therapy among older men with symptomatic hypogonadism was associated with significantly greater increase in coronary artery noncalcified plaque volume [68].

Augmentation of primary drugs with testosterone or testosterone replacement therapy could be used to treat anxiety, depression, neurodegenerative disorders or type 2 diabetes in some groups that meet narrow criteria, but the results of some studies remain controversial. To ensure safety of treatment augmentation with testosterone replacement therapy extensive long-term controlled clinical trials are still required.

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