Testosterone, depression, and cognitive impairment in men: an attempt at practical analysis.

B.M. Vornyk
Kyiv Research Center of Sexology, Andrology and Reproduction

Cognitive impairment (CI) accompanies the aging process and is manifested by difficulties with memorization, learning, concentration and decision-making, which greatly complicates the daily life of the suffering subject. In addition, medical care and social adaptation of these patients are costly and put a significant strain on the health care system. According to a forecast by G. Corona’s group, the number of people with CIs will increase significantly in the coming years, reaching 131.5 million by 2030. To date, a significant amount of researches has been conducted to uncover the mechanisms of development and risk factors of CI in order to develop effective prevention and treatment programs. Age-related decline in testosterone levels are among the potentially modified risk factors of CI.

The objective: to analyze the role of testosterone in pathogenesis of cognitive impairment and depression and the possibilities of testosterone therapy to correct them.

Materials and methods. Evidence was collected from the study publications and meta-analyses exploring the role of testosterone in pathogenesis, prevention and correction of cognitive impairment and depression over the past five years and preliminary analysis of data from our own study involving 547 men with hormonal disorders.

Results. Cerebral vessels are the target for the direct (via androgen receptors) and indirect (via influence on cardiovascular risk factors) action of androgens. The testosterone insufficiency is associated with both metabolic and cardiovascular disorders (hypertension, diabetes, hyperlipidemia, obesity), as well as depression and CI. Serum-free-testosterone and free testosterone index are the most sensitive biomarkers of testosterone insufficiency in patients with depression and CI. The corrective effect of testosterone therapy (TT) on depression and CI depends on their severity and levels of androgens: a clinically and statistically significant effect was registered in mild disorders with androgen deficiency.

Despite the importance of androgens for mood and cognitive functions, and their synchronous decline during the aging process, the place of TT in the prevention/correction of whole spectrum of CIs is still unclear. It is obvious now that TT can be justified in patients with mild disorders and proven androgen signal attenuation, but in most cases has no independent meaning. Further studies to find optimal TT indications and regimes are mandatory.

Conclusions. Despite the importance of androgens for mood and cognitive functions, and their synchronous decline during the aging process, the place of TT in the prevention/correction of whole spectrum of CIs is still unclear. It is obvious now that TT can be justified in patients with mild disorders and proven androgen signal attenuation, but in most cases has no independent meaning. Further studies to find optimal TT indications and regimes are mandatory.

Keywords: cognitive impairment, dementia, depression, brain, testosterone, therapy.
Тестостерон, депрессия и когнитивные нарушения у мужчин: попытка практического анализа Б.М. Ворник

Когнитивные нарушения (КН) сопровождают процесс старения и проявляются трудностями с запоминанием, обучением, концентрацией внимания и принятием решений, что значительно усложняет повседневную жизнь страдающего в патогенезе, профилактике и коррекции когнитивных нарушений и депрессии за последние пять лет, а также предварительного анализа данных собственного исследования с участием 547 мужчин с гормональными нарушениями.

Результаты. Сосуды головного мозга являются мишенью для прямого (влияя на андрогенные рецепторы) и опосредованного (влияя на сердечно-сосудистого риска) действия андрогенов. Недостаточность тестостерона связана как с метаболическими, так и с сердечно-сосудистыми нарушениями (артериальная гипертензия, сахарный диабет, гипертрихоз, окклюзия, ожирение), а также с депрессией и КН. Сывороточный свободный тестостерон и индекс свободного тестостерона являются наиболее чувствительными биомаркерами недостаточности тестостерона у пациентов с депрессией и КН. Коррелирующее действие терапии тестостероном (ТТ) на депрессию и КН зависит от их выраженности и уровня андрогенов: клинически и статистически значимый эффект зарегистрирован при легких расстройствах на фоне андрогенного дефицита. Результаты мета-анализа не дают оснований для использования ТТ для улучшения внимания, памяти (рабочей, вербальной, зрительной), исполнительной функции, речи, зрительно-моторных и зрительно-пространственных способностей у субъектов с эугонадизмом и гипогонадизмом. Согласно предварительному анализу результатов данного исследования, характер психоэнзима андрогенных нарушений определяется половой конституцией (ПК): слабый тип ПК (женское мужчины) связан с более высокой частотой тревожности, сильный тип ПК – со склонностью к депрессии, промежуточный тип ПК – с андрогенами. Таким образом, у пациентов с андрогенной следует измерять уровень тестостерона, эстрогенов, адреналина и кортизола.

Заключение. Вместе с тем вопросы влияния андрогенов для наступления и когнитивных функций и синхронность их снижения в процессе старения, место ТТ в профилактике/коррекции всего спектра КН остается неясным. Сегодня очевидно, что ТТ может быть оправдана у больных с легкими нарушениями и доказанным и порогам андрогенного сигнала, но в большинстве случаев не имеет самостоятельного значения. Необходимы дальнейшие исследования для поиска оптимальных показаний и режимов ТТ.

Ключевые слова: когнитивные нарушения, деменция, депрессия, мозг, тестостерон, терапия.

In addition, many other factors increase the risk of depression, dementia, and cognitive disorders, such as marital status, social activity, educational level, physical activity, smoking, alcohol abuse, hypertension, obesity, diabetes mellitus, hormonal disorders, including hypogonadism. Blood vessels play a crucial role in the pathogenesis of depression, cognitive impairment, and dementia, especially the state of the brain’s vascular network.

In recent years, the results of scientific research have paid more and more attention to the indirect pathways of testosterone’s effects on the body, including cognitive disorders [3]. And some preclinical and clinical data indicate a possible contribution to the development of cognitive impairment age-related decline in testosterone [1].
Over the past decades, interest in the ability of testosterone to influence the development or course of depression has grown significantly. There have been many different studies in the scientific literature on the effects of Testosterone replacement therapy (TRT) on cognitive impairment and depression.

A review of scientific publications and meta-analyses over the past five years demonstrates a lack of consensus on the role of testosterone in the prevention and correction of depression and cognitive impairment, including dementia. C. Abi-Ghanem, L.S. Robison and K.L. Zuload [4] in their study demonstrated that androgens affect the vasculature of the brain. Moreover, the cerebral vasculature is a target for the direct action of androgens since it expresses several sex steroid receptors and metabolizing enzymes. But at the same time, the action of androgens on the vasculature of the brain is complex, as they have been shown to have both protective and harmful effects depending on age, dose of androgens, and process of disease.

In addition to the direct effects of androgens on the brain’s vasculature, androgens also affect other vascular risk factors. In men, low androgen levels are closely associated with metabolic and cardiovascular diseases, including hypertension, diabetes, hyperlipidemia, and obesity, which significantly increase the risk of stroke and VCID. Thus, a better understanding of the interaction of androgens with the brain’s vasculature in physiological and pathological conditions are of key importance.

In a study conducted by M. Zitzmann [5], a significant positive effect of TRT was obtained in patients with depression, anxiety, and cognitive impairment compared with the placebo group, the positive mechanism of action of which is explained by the indirect effect of testosterone through improved blood flow, the formation of stress resistance and impact on the reward system. Meta-analysis of random effects of 27 RCTs, including 1890 men [6], showed that testosterone treatment is associated with a significant reduction in depressive symptoms compared with placebo. Meta-regression models suggest a significant interaction of testosterone treatment with different dosages and symptom variability at baseline.

At the same time, a 2020 study by Z. Chen, X. Shen, K. Tian et al. [7] was aimed at determining the relationship between serum testosterone levels and symptoms of depression in the adult male population. A survey of 1166 men found that the mean levels of total testosterone, sex hormone-binding globulin, and luteinizing hormone were significantly higher in the group with depressive symptoms than those without depression. However, serum-free-testosterone and free testosterone index (FTI) was significantly lower in the depressive group than in the non-depressed group. In addition, the mean FTI was negatively correlated with the Beck Depression Scale score in the multiple linear regression model (95% CI: 3.274 to 0.406). Based on the results, the authors conclude that it is the decrease in the level of bioavailable testosterone that may be a factor in depression in adult men, and FTI may be the most sensitive biomarker reflecting the level of bioavailable testosterone in patients with depression. At the same time, there is a connection between testosterone and TAU protein level [8]. Many indications point to an association between low testosterone levels, poor cognitive function, and a high risk of AD, and these associations are more pronounced in men than in women.

In a review of small placebo-controlled RCTs, A. Kielan, D. Gorostiza, A. Mosio et al. [9] investigated the effect of testosterone replacement therapy (TRT) on depression symptoms in patients with late-onset testosterone deficiency. In patients with mild clinical depression, TRT has been shown to reduce symptoms of depression, except for patients with major depressive disorder. This effect was not observed in men with severe depressive disorders. In non-depressed patients, TRT decreases depressive symptom scores; however, the clinical value is challenging to measure.

According to the results of longitudinal studies, other researchers share a similar opinion on the conflicting effect of testosterone on depression. The unclear association between sex hormones and symptoms of depression according to the results of longitudinal studies is shared by other researchers [10, 11, 12].

At the same time, in their work, C.R. Buskbjerg, C.H. Gravholt, H.R. Dalby, and co-authors give an opposite opinion [13]. They analyzed a systematic review and meta-analysis of TRT and male cognitive functioning. They noted that TRT does not improve cognitive function in men with normal testosterone levels and has a controversial improvement in cases of testosterone decline. The authors point out that there is no justification for prescribing testosterone for cognitive impairment, especially in the absence of clinical signs of hypogonadism.

The work of G. Corona et al. is of great interest [14], in which authors summarized and discussed all the information obtained from the available experimental studies in animals. In addition, they performed a meta-analysis of data from all randomized, placebo-controlled trials (RCTs) published to date. The authors concluded that only limited preclinical and clinical data could confirm the possible contribution of testosterone to the pathogenesis of age-related cognitive impairment. In addition, the meta-analysis did not support the use of T-replacement therapy to improve several cognitive areas analyzed, including attention, working memory, executive function, language, verbal memory, visual memory, visual-motor, and visual-spatial abilities. The study notes that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism, which does not allow a definitive conclusion on these issues. In the study of Testosterone by mass spectrometry (gold standard), there was no association between age-dependent decrease in Testosterone and memory problems [1].

Even though the analysis of scientific studies over the past five years showed still quite controversial and conflicting results, there were more positive results, where TRT reduced the symptoms of depression in men with hypogonadism. Testosterone demonstrated a higher efficiency in minor affective disorders, dysthymia, depressive symptoms [9].

In the current research of the Kyiv Scientific Center for Sexology, Andrology, and Reproduction, the influence of sex hormones and some neurotransmitters on the clinical, psychological, and socio-behavioral characteristics of healthy men and women, as well as patients with hypogonadism, depending on the type of sexual constitution, is currently being studied.
The following psycho patterns are studied:
- Masculinity and femininity;
- Social success profile;
- Cognitive analytical skills;
- Emotional profile;
- Aggression and Sexual Behavior.

The following methods were chosen for the study: Masculinity and femininity by Bem, S.L. Sex-role inventory; Profile of Social Success: Purpose-In-Life Test, PII by Crumbaugh & Maholick; Cognitive and analytical skills: Objects Excluding, The Process of Education by J. Bruner; Emotional profile and personal characteristics: 'Toronto alexithymia scale by G.J. Taylor, Mini-Mult Questionnaire, State-Trait Anxiety Inventory – STAI, Zung Self-Rating Depression Scale, Leonard-Smishke’s ‘characterological’ questionnaire; Aggressiveness by Buss-Durkee Hostility Inventory: Assessment of aggressiveness in the relationship by A. Assinger.

When assessing the effect of hormones on the psychosexual state, the recommendations of John Money (J. Money, 1972) were taken into account, namely: stage of the life cycle of an organism, the nature of the hormones administered and their ratio, the amount of the hormone, its daily and rhythmic fluctuations, the biological activity of the hormone, time and duration of hormonal exposure, pathways of hormone circulation, features of methods for measuring hormone levels and assessing hormone-dependent behavioral responses, as well as age, sexual constitution, psychological gender, psychosexual personality type [14].

The study is ongoing, but a preliminary assessment of the results obtained with 199 healthy men and 547 men with hormonal disorders reveals some trends. So, there is a clear dependence of sexually-psychological behavior and sexual role on the type of sexual constitution (SC) – (strong, medium, weak type) and the level of testosterone in the blood of healthy men. The social success profile is highest in men with a strong SC type (masculine men), and the level of creativity is the highest (in an average SC type (androgyneous men).

The level of anxiety is highest in the weak type of SC (feminine men), and the propensity for depression is higher in the strong type of SC. The level of aggression is highest in men of the middle type of SC, which requires special attention to the role of androgens, estrogens, vasopressin, and adrenaline in the occurrence of aggression.

Research Results will be published after completed surveillance, and detailed analysis of statistical data processing.

Although TRT’s effect on cognitive function in men with hypogonadism remains controversial, testosterone in clinical practice always shows a subjective improvement in mood, performance, exercise tolerance, an increase in social activity, and an improvement in sexual function, regardless of the age of men.

In studying the effect of testosterone on depressive and cognitive disorders in men, it makes sense to combine the efforts of andrologists, psychiatrists, and medical psychologists for the correct design of studies and taking into account different forms and variants of disorders based on the ICD.11.

REFERENCES

1. Corona G, Guarraldi F, Rastrelli G, Sforza A, Miggi M. Testosterone deficiency and risk of cognitive disorders in aging males. World J Mens Health. 2021;39(1):9-18. doi: 10.5534/wjmh.200017.
2. Kuo CY, Stachiv I, Nikolai T. Association of late life depression, (Non-) modifiable risk and protective factors with dementia and Alzheimer’s disease: literature review on current evidences, preventive interventions and possible future trends in prevention and treatment of dementia. Int J Environ Res Public Health. 2020;17(20):4745. doi: 10.3390/ijerph17204745.
3. Morgenstaller A, Traish A, Hackett G, Jones TH, Ramasamy R. Diagnosis and treatment of testosterone deficiency: updated recommendations from the Lisbon 2018 International Consultation for Sexual Medicine. Sex Med. Rev. 2019 Oct;7(4):656-60. doi: 10.1016/j.sxmr.2019.06.003.
4. Ali-Ghanem C, Robinson LS, Zaloga KL, Ab-Ghanem M. Androgens effects on cerebrovascular function in health and disease. Biol Sex Diff. 2020 Jun 30;11(13). doi: 10.1186/s12329-020-00309-4.
5. Zibtmann M. Testosterone, mood, behavior, and quality of life. Androl. 2020;3(6):1598-605. doi: 10.1111/andr.12867.
6. Walther A, Breidenstein J, Miller R. Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis. JAMA psychiatry. 2019;76(1):31-40. doi: 10.1001/jamapsychiatry.2018.2734.
7. Chen Z, Shen X, Tian K, Liu Y, Xiong S, Yu Q, et al. Bioavailable testosterone is associated with depression in adult men. J Int Med Res. 2020;48(8):0300062920941715. doi: 10.1177/0300062920941715.
8. Sundaram E. E. , Panizzon M. S., Chen X, Andrews M, Galasko D, Banks SJ , et al. Alzheimer’s disease neuroimaging initiative. sex differences in Alzheimer’s related tau biomarkers and a mediating effect of testosterone. Biol Sex Diff. 2020;11(1):33. doi: 10.1186/s12329-020-00310-x.
9. Kielan A, Gorostiza D, Mosiolen A, Chodkiewicz J, Swicki L, Walewska-Zielecka B. Depression in males-specificity, aetiology, relationships with suicidal tendencies and the psychoactive substances usage: literature overview. Adv Psychiatry Neurol. 2020;29(1):54-66. doi: 10.5114/ppn.2020.94695.
10. Shah Syed AA, He L, Shi Y. The potential effect of aberrant testosterone levels on common diseases: A Mendelian Randomization Study. Genes. 2020;11(7):2721 doi: 10.3390/genes11070271.
11. Kische H., Gross S., Wallaschekd H. Grabe HJ, Völde H, Nauck M, et al. Associations of androgens with depressive symptoms and cognitive status in the general population. PLoS One. 2017;12(5):e0177272. doi: 10.1371/journal.pone.0177272.
12. Jung HJ, Shin HS. Effect of Testosterone Replacement Therapy on Cognitive Performance and Depression in Men with Testosterone Deficiency Syndrome. World J Mens Health. 2016;34(3):199-9. doi: 10.5534/wjmh.2016.34.3.194.
13. Buskiberg CR, Grawholt CH, Dalby HR, Amidt A, Zachariae R. Testosterone supplementation and cognitive functioning in men—a systematic review and meta-analysis. J Endocr Soc. 2019;3(6):1465-84. doi: 10.1210/js.2019-00119.
14. Vornyk BM, Kryshtal EV. Sexopatologia: textbook for doctors. Kyiv: Medicina; 2013. 552 s.