REVIEW

TESTOSTERONE THERAPY, NEW OPPORTUNITIES IN DIABETES MELLITUS

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Abstract

Diabetes mellitus is at the moment a real public health problem worldwide. It is estimated that at least one-third of male patients with type 2 diabetes mellitus also have associated testosterone deficiency. In this context, the opportunity for testosterone medication in patients with hypogonadism and type 2 diabetes mellitus becomes very attractive if we also take into account its pleiotropic effects on the metabolic syndrome. As it has been demonstrated, the low level of testosterone is associated with an increase in cardio-metabolic risks, which lead to increased premature mortality. Testosterone therapy is relatively safe, having potential benefits as long as the cases are carefully selected and its positive effects on the metabolic status recommend this therapy as an interesting option in patients with documented diabetes mellitus and hypogonadism.

Rezumat

Diabetul zaharat este în prezent o problemă reală de sănătate publică la nivel mondial. Se estimează că cel puțin o treime dintre pacienții de sex masculin cu diabet zaharat de tip 2 au asociat o deficiență a testosteronului. În acest context, oportunitatea pentru medicația cu testosteron la pacienții cu hipogonadism și diabet zaharat de tip 2 devine foarte atractivă dacă luăm în considerare și efectele sale pleiotropice asupra sindromului metabolic. După cum s-a demonstrat, nivelul scăzut de testosteron este asociat cu o creștere a riscurilor cardio-metabolice, ceea ce duce la creșterea mortalității premature. Terapia cu testosteron este relativ sigură, având beneficii potențiale atât timp cât cazurile sunt atent selectate, iar efectele sale pozitive asupra stării metabolice recomandă această terapie ca o opțiune interesantă la pacienții cu diabet zaharat și hipogonadism documentat.

Keywords: testosterone, hypogonadism, diabetes mellitus, metabolic syndrome

Introduction

As it is already known, diabetes mellitus is already considered a global epidemic, with approximately 422 million people over the age of 18 having already been diagnosed until 2014, while the estimated figure is of 592 million diabetic patients by 2053 [1]. Overweightness and obesity continue the ascending trend so that 1 out of 3 adults aged 18+ is already overweight and 1 out of 10 obese, according to the data provided by WHO in 2014 [1, 2]. In the United States, one-third of the male population over 65 have type 2 diabetes mellitus and similarly, one-third have testosterone deficiency, compared to young healthy men. Similar data are also reported in Europe, so the decrease in testosterone level in relation to age becomes a global phenomenon, which is more frequently seen in elderly men who also have diabetes mellitus [3-6].

A significant number of epidemiologic studies have demonstrated the correlation between obesity, the metabolic syndrome and dysglycaemia with low testosterone levels in patients with type 2 diabetes mellitus [7]. This correlation is of a particular

importance since low testosterone level in men is known to be associated with the increased cardio-metabolic risk by increasing the incidence of dyslipidaemia and atherosclerosis, factors which lead to increasing premature mortality [8]. The metabolic syndrome plays an important role in testosterone homeostasis through its components: insulin resistance, central type obesity, hypertension, dyslipidaemia, the pro-inflammatory and the pro-thrombotic status; its low level and the decrease in sex-hormone binding globulin (SHBG) being predictive factors for the metabolic syndrome. In this context, we can say that the low testosterone level could be a predictive factor for the metabolic syndrome and for diabetes mellitus and a significant cardio-vascular risk factor. Mortality due to cardiovascular causes is twice more increased in men than in women, this correlation being valid for all age groups, while the difference between genders being precisely the testosterone profile [9].

The metabolic syndrome and diabetes mellitus in relation with testosterone

As studies have shown, the correction of low testosterone levels in elderly diabetic patients would lead to a significant improvement in overall glycaemic and metabolic control. This aspect could be a revolutionary breakthrough that might place the therapeutic correction of testosterone level among the common therapies for diabetes mellitus, and the assessment of the androgenic function could be an important element in the management of diabetes mellitus. There is a series of data to support such concepts which, on the one hand, show the connection between the low testosterone level and the occurrence of diabetes mellitus and, on the other hand, the improvement of glucose metabolism along with the improvement in testosterone status. A meta-analysis by Ding *et al.* in 2006 shows that diabetic men have a significantly lower testosterone level compared to men of the same age, but who do not have diabetes. The mean difference in testosterone levels between the two groups was -76.6 ng/dL (CL95%, confidence interval between -99.4 ng/dL and -53.5 ng/dL). Moreover, it seemed that men with a high testosterone level (449.6 - 605.2 ng/dL) showed a decrease in the incidence of diabetes mellitus by 42% compared to those who had low testosterone levels (213 - 446 ng/dL) [10]. The low level of SHBG was associated with an increased risk of diabetes mellitus, data also confirmed by Perry and Lakshman in their studies, considering it a predictive factor in the occurrence of diabetes [10]. However, there are studies that have found that the relationship between testosterone level and insulin-resistance or the metabolic syndrome is independent from the SHBG value [11].

The Third National Health and Nutrition Examination Survey show that men with low testosterone level have increased incidence of type 2 diabetes mellitus compared to the control group. The study on hypogonadism in males, which involved 1849 men (398 diabetics) highlighted the relationship between obesity and low testosterone levels, a reversed correlation between testosterone and the body mass index (BMI) even though the patients had or not diabetes. In particular, diabetic patients exhibited the lowest levels of testosterone [12-14].

Recent studies attempt to indicate the relationship between atherosclerosis, hypertension, diabetes mellitus, inferior urinary tract pathology and erectile dysfunction and, especially, to demonstrate that these pathological entities do not differ in aetiology, but, on the contrary, require an integrated approach in the elderly patient. The diagnosis and treatment of testosterone deficiency should thus become an integrated component of the elderly pathology. The elderly patient is also the one who has both diabetes mellitus and the metabolic syndrome, while the erectile dysfunction and prostatic pathology are clearly associated.

The incidence of the metabolic syndrome has increased steeply in both Western countries and in the USA, while abdominal obesity, the metabolic syndrome marker are the cause of disturbances in the metabolism of free fatty acids. They have a much higher portal flow and induce metabolic disorders by affecting hepatic metabolism in case of abdominal obesity. Free fatty acids are activated by the nuclear factor kB, increasing the synthesis of tumour necrosis factor α (TNFα) which subsequently activates lipolysis, increasing the synthesis of interleukin 6 and of chemoattractant macrophages that will actively modulate insulin sensitivity. The tumour necrosis factor α thus contributes to the modulation of both insulin sensitivity and endothelin-1, promoting vasoconstriction. The fatty steatotic liver is directly correlated with the presence of metabolic syndrome components, this being a key factor in insulin-resistance pathogenesis. The peptides and cytokines secreted by visceral adipocytes are responsible for the accumulation of fat in the liver, their level being correlated with the occurrence of elevated values of C reactive protein (CRP). Pro-inflammatory factors such as interleukin 6, interleukin 1β, plasminogen activator inhibitor -1, tumour necrosis factor α (TNF α), angiotensinogen, vascular endothelial growth factor and serum amyloid A are secreted at the level of visceral adipocytes, factors which determine both systemic and peripheral inflammation and eventually organ dysfunction [15, 16, 17]. The free testosterone is

reversely correlated with the obesity index, suggesting that visceral adiposity levels dictate its value due to the increased aromatase-mediated oestrogen conversion, which has an inhibitory effect on the gonadal-hypothalamic-pituitary axis.

The hypothesis of obesity-adipocytokine-hypogonadism could clarify why the organism does not increase testosterone secretion by increasing the levels of gonadotropins. Oestradiol, TNFα, interleukin 6 inhibits the production of GnRH, lowers the secretion of FSH (follicle stimulating hormone) and LH (luteinizing hormone) at pituitary level, thus leading to the decrease in gonadal stimulation. This hypothesis is moreover interesting since leptin, as already known, stimulates GnRH and induces a decrease in LH release. Leptin has a significant role in maintaining body weight and on appetite/ food intake [20-24]. In obesity, adipocytes release an increased amount of leptin and thus the resistance of hypothalamic-pituitary axis occurs. The direct mechanism of leptin makes its action inhibit the activity of gonadotropins at the level of Leydig cells and lowers testosterone secretion. Therefore, leptin can be said to have the role of diminishing the androgenic status in obesity [25-29].

In fact, in patients with metabolic syndrome, the increase/decrease in body weight is associated with the increase/decrease of insulin level, with the decrease/ increase in SHBG, with the decrease/increase in plasma testosterone levels; weight loss actually proves to have a beneficial effect on the metabolic syndrome and also on the testosterone level.

Studies on the relationship between the low testosterone level and diabetes mellitus showed a reversed association with the glycosylated haemoglobin level (HbA1c) [18, 19]. Longitudinal epidemiological studies prove that the low testosterone level is a unilateral predictor of both metabolic syndrome and diabetes mellitus [20]. The study conducted by Dhindsa *et al.* in 2016 showed that therapy with testosterone increased insulin sensitivity, decreased blood glucose levels *à jeun* and improved metabolic parameters even though there were no significant changes in HbA1C (the authors state that the study was too short to be relevant in this perspective) [21].

The Massachusetts Male Aging Study and Multiple Risk Factor Intervention Trial provide information on the status of SHBG and also testosterone and conclude that these are independent predictive factors in the development of diabetes mellitus in middle-aged men, the low testosterone level being a risk factor even for patients who were not initially obese. The Rancho-Bernardo Study and another Finnish study show that there is a reversed correlation between the "baseline" level of testosterone and the evolution of blood glucose and insulin levels *à jeun*, thus concluding that it is involved in both the prediction of the metabolic syndrome and also of diabetes mellitus. There are also observations on the relationships between testosterone levels in patients with type 1 diabetes mellitus. The study included patients with type 1 diabetes mellitus and a normal testosterone level and patients with type 2 diabetes mellitus but with suboptimal testosterone values. The results were set due to the difference between the levels of circulating insulin (decreased in type 1 and increased in type 2). A reversed correlation between the level in insulin and SHBG has also been found, following low testosterone levels in patients with type 2 diabetes mellitus [22]. Chronic metabolic imbalance in diabetes and hyperglycaemia directly influence the level of testosterone in Leydig cells apparently through a direct mechanism, since there are insulin receptors at this level. On the other hand, the coexistence of hypogonadism in diabetes mellitus seems to be due to a decrease in LH secretion and the alteration of its glycosylation, as a secondary mechanism.

A series of studies have noticed the simultaneous occurrence of type 2 diabetes mellitus and hypogonadism and an association between the overall testosterone level in the plasma and the development of type 2 diabetes mellitus. Studies indicate that, in the presence of diabetes mellitus, testosterone was 10 - 15% lower than in healthy people in the same age group. Experimental studies indicate the importance of the functional state of the gonads in carbohydrate metabolism since hyperglycaemia, glycosuria, lower glucose tolerance and insulin sensitivity are noticed in castrated animals. Gonadal disorders are often noticed in both diabetic men and women. The frequency of sexual function disturbances in men with diabetes mellitus varies between 24.7 and 74%. Spermatogenesis disorders are reported in patients with diabetes mellitus (DM) who do not follow an appropriate treatment, and they are expressed by decreasing the percentage of active spermatozoa. The coexistence of microangiopathic and polyneuropathic complications in patients with diabetes mellitus (DM) depresses even more the sexual function on the whole. A direct correlation between the length of DM, its degree and the patients' age was noticed and, on the other hand, the decrease or lack of potency and libido.

Cardiovascular disease and testosterone

New data in the literature show that the low testosterone level and the presence of diabetes mellitus are predictive factors for cardiovascular diseases (CVD). As already known, diabetes mellitus is a significant risk factor for CVD. In its turn, CVDs are one of the most important causes of morbidity and mortality in male diabetic patients. However, a series of studies indicate that the

association between the low testosterone level and the presence of diabetes mellitus multiplies the risk for CVD, while hypotestosterone itself is an independent coronary and endothelial dysfunction risk factor. As shown in Osteoporotic Fractures in men Study in Sweden, the cohort of patients with low testosterone level had multiple cardiovascular risk factors compared to the patients with a normal/ increased testosterone level. (HR = 0.70, 95% CI 0.56 - 0.88, p = 0.002) [10, 31]. Japanese studies presented similar data, the cohort of 171 middle-aged patients with coronary risk factors and low testosterone levels, had a 25% increased risk of cardiovascular events compared to patients with present coronary risk factors, but an optimal testosterone level ($p < 0.029$) [32-34].

As already known, heart failure (HF) also affects skeletal muscles, the immune and the endocrine systems. HF is characterized by elevated serum cortisol levels, increased immune activation associated with low levels of anabolic hormones and insulin growth factor (IGF)-1. Consistent data suggest that patients with HF have both insulin-resistance and resistance to growth hormones. This metabolic context favours catabolism and loss of muscle mass, decreases effort and physical exercise capacity. Testosterone is an independent factor of increasing mortality in men with HF when its level is suboptimal. Low testosterone levels are present in all NYHA degrees of HF classification, its values decreasing with the aggravation of HF. On the other hand, the lower the testosterone level, the lower the physical performance. The presence of testosterone receptors at the myocardial level indicates the hypothesis that testosterone has a direct impact on cardiac remodelling and on the renin-angiotensin-aldosterone axis, contributing directly to the occurrence of HF or even congestive heart failure [34, 41-43]. Interventional studies show that therapeutic intervention used to correct testosterone levels in patients with HF resulted in progressive improvements in physical effort resistance but, on a short term, did not have any effect on the muscles (3 - 6 month studies). Moreover, an improvement in insulin sensitivity and bio-impedance parameters was noticed (decreased fat mass and increased body weight) [34, 35]. However, testosterone therapy, in the absence of physical exercise does not seem to have any benefit on the wasting syndrome present in HF. Recommendations include the progressive increase in the effort capacity associated with testosterone therapy, the improvement of bio-impedance parameters (decrease in fat mass and increase in muscle mass) and the reduction or prevention of dyspnoea in elderly patients with HF [36, 37].

Testosterone is also actively involved in atrial pathology. Atrial fibrillation (AF) is one of the most common arrhythmias which are associated with an increased risk of morbidity and mortality. A few small studies have revealed that low overall testosterone levels are associated with the increased incidence of AF. On the other hand, the incidence and prevalence of AF increases with age in both men and women. The mechanism that differentiates the incidence in the two sexes is still unknown. Testosterone therapy reduces the risk of AF, while, surprisingly, the anabolic steroidal therapy seems to be associated with an increased risk of AF. Sharma *et al.* investigate in his study a cohort of 76,639 veterans with a low testosterone level. He divided the cohort into 3 groups: the first group received testosterone therapy until normalization of the values (40,856 patients, average age of 66 years); the second group received testosterone therapy, but optimal serum values were not reached (23,939 patients with an average age of 65 years); the third group did not receive testosterone therapy (11,853 patients with an average age of 67 years). The results showed a reduced risk of AF for the 2nd group compared to the 1st one (HR 0.90, 95% Cl 0.81 - 0.99, p = 0.0255) and the 3rd (HR 0.79, 95% Cl 0.70 - 0.89, p = 0.0001). The normalization of testosterone levels after the medical intervention decreased significantly the risk of AF [38].

The results of the study conducted in Sweden and presented by the European Association for Study of Diabetes in 2013 showed a reversed correlation between testosterone levels and the incidence of myocardial infarction (MI). The diabetic patients with a normal testosterone level had a significantly reduced risk of MI compared to the diabetics who had a low testosterone level even after age adjustment (HR 0.75, p = 0.006) [39-41].

More extensive studies conducted on Caucasian population confirm the reverse relationship between testosterone levels and age, metabolic syndrome and CVD. The low testosterone level is also correlated with decreasing the carotid mean intimate index independently from the body mass index, waist-hip ratio, high blood pressure, the presence of type 2 diabetes mellitus and dyslipidaemia [42, 43].

Testosterone is also an active player in the pro-thrombotic state. The fact that high testosterone levels have a positive influence on haematocrit concentration is not clear yet, thus increasing the risk of venous thrombosis, although it is known that one of the adverse reactions of testosterone administration is the increase of haemoglobin and haematocrit levels. Testosterone therapy has not been associated with a high risk of thrombo-embolism despite the plausible opinion that a high haematocrit level is a risk factor for CVD occurrence. According to the Endocrine Society, a haematocrit value higher than 54% is a relative contraindication of testosterone therapy. That is why it is recommended that the haematocrit should be evaluated during

testosterone therapy at treatment initiation and then after 3 months, 6 months and then annually. The European Association of Urology recommends the concomitant administration of aspirin or the reduction of testosterone dose during testosterone therapy in case the haematocrit exceeds 54%, since the benefits are higher than the risks [44]. As suggested above, low testosterone in men is associated with the increase of pro-thrombotic factors, irrespective of the age, degree of obesity, distribution of the adipose tissue or the presence of other metabolic syndrome parameters. This aspect could be due to the fact that testosterone therapy leads to lowering lipoprotein A level (LpA) with almost 20 - 50%. LpA is a thrombotic risk factor itself especially in the presence of V Leiden factor, the low testosterone level additionally increasing the risk. The low testosterone level in men is negatively correlated with PAI 1 (plasminogen activator inhibitor) and factor VII and positively with tPA (tissue plasminogen activator). In this context, hypogonadism is associated with the risk of hyper-coagulability [44, 48]. It is interesting that erythrocytic anomalies have been observed during long-term testosterone therapy, but improved membrane composition and viscosity have also been noticed, aspects which reduced the risk of thrombosis. In Testosterone's effects on atherosclerotic progression in aging man, 155 men were treated with testosterone for 3 years, 8% of whom had a haematocrit higher than 54% in this period. The incidence of increased haematocrit values is low, thus being no risk in treating patients with hypogonadism [45-47, 50].

At present, the inferior limits of testosterone levels that require the administration of a hormonal substitution therapy have not been precisely established. The therapy cannot be given depending on the symptoms of the patient, even if these seem suggestive for testosterone deficiency or interfere with the sexual activity of the individual, because they are not specific and may occur as men grow older. Current trends suggest that testosterone therapy is relatively safe, with potential benefits as long as the cases are carefully selected, especially those with atherosclerotic vascular disease history. The intrinsic connection between testosterone deficiency and diabetes mellitus is surely obvious, moreover in case of type 2 diabetes mellitus, metabolic syndrome, dyslipidaemia, athero-sclerosis and CVD. Its pleiotropic effects place testosterone on a higher level in the therapy associated with these pathologies. Of course, a large number of studies is necessary, especially those which target the occurrence of cardiovascular events during testosterone therapy, which can be more effectively dosed in order to prevent such adverse effects. Until the presentation of further data, clinicians should reconsider testosterone levels in pathology, be cautious when it comes to the adverse effects related to cardiovascular events and carefully document and select cases [48-50].

Conclusions

The obvious question is whether testosterone therapy is a therapeutic option in men with hypogonadism and type 2 diabetes mellitus. It is still a question with no clear answer. The European Endocrinology Association indicates the prescription of testosterone treatment in patients with no previous cardio-vascular events, but it does not clearly specify, nor clarify which. Further recommendations to be found in guides need serious long-term studies so that testosterone therapy to be safe, standardized and based on the individual risk model.

References

1. Danaei G, Finucane MM, Lu Y, National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys participants. *Lancet*, 2011; 378: 31-40.
2. WHO Mortality Database. Geneva: World Health Organization; http://apps.who.int/healthinfo/statistics/mortality/causeofdeath_query/.
3. Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, Bainbridge KE, Fradkin JE, Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. *Diabetes Care*, 2010; 33(5): 62-68.
4. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab.*, 2001; 86: 24-31.
5. Shaw JE, Sicree RA, Zimmet PZ, Global estimates of the prevalence of diabetes for 2010 and 2030. *Diab Res Clin Pract.*, 2010; 87: 4-14.
6. Orwoll ES, Nielson CM, Labrie F, Barrett-Connor E, Cauley JA, Cummings SR, Ensrud K, Karlsson M, Lau E, Leung PC, Lunggren O, Mellström D, Patrick AL, Stefanick ML, Nakamura K, Yoshimura N, Zmuda J, Evidence for geographical and racial variation in serum sex steroid levels in older men. *J Clin Endocrinol Metab.*, 2010; 95: E151-E160.
7. Schipf S, Haring R, Friedrich N, Nauck M, Lau K, Alte D, Stang A, Völzke H, Wallaschofski H, Low total testosterone is associated with increased risk of incident type 2 diabetes mellitus in men: results from the Study of Health in Pomerania (SHIP). *Aging Male*, 2011; 14: 168-175.
8. Araujo AB, Kupelian V, Page ST, Handelsman DJ, Bremner WJ, McKinlay JB, Sex steroids and all-cause and cause-specific mortality in men. *Arch Intern Med.*, 2007; 167: 1252-1260.
9. Stanworth RD, Jones TH, Testosterone in obesity, metabolic syndrome and type 2 diabetes. *Front Horm Res.*, 2009; 37: 74-90.

10. Ding EL, Song Y, Malik VS, Liu S, Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*, 2006; 295(11): 1288-1299.
11. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT, Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care*, 2004; 27: 1036-1041.
12. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, Dobs A, Basaria S, Golden SH, Platz EA, Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care*, 2007; 30: 234-238.
13. Brand JS, Wareham NJ, Dowsett M, Folkerd E, van der Schouw YT, Luben RN, Khaw KT, Associations of endogenous testosterone and SHBG with glycated haemoglobin in middle-aged and older men. *Clin Endocrinol (Oxf.)*, 2011; 74: 572-578.
14. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, Zajac JD, Jerums G, Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab.*, 2008; 93: 1834-1840.
15. Velescu BS, Anuţa V, Aldea A, Jinga M, Cobeleschi PC, Zbârcea CE, Uivarosi V, Evaluation of protective effects of quercetin and vanadyl sulphate in alloxan induced diabetes model. *Farmacia*, 2017; 65(2): 200-206.
16. Stanworth RD, Kapoor D, Channer KS, Jones TH, Androgen receptor CAG repeat polymorphism is associated with serum testosterone levels, obesity and serum leptin in men with type 2 diabetes. *Eur J Endocrinol.*, 2008; 159(6): 739-746.
17. Drăgoi CM, Nicolae AC, Grigore C, Dinu-Pîrvu CE, Arsene AL, Characteristics of glucose homeostasis and lipidic profile in a hamster metabolic syndrome model, after the co-administration of melatonin and irbesartan in a multiparticulate pharmaceutical formulation. The 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications, INTERDIAB 2016, 3-5 March, Bucharest, Romania, Diabetes Mellitus as Cardio-vascular Disease, Ed. Niculescu Bucureşti, 221-229.
18. Stanworth RD, Jones TH, Testosterone in obesity, metabolic syndrome and type 2 diabetes. *Front Horm Res.*, 2009; 37: 74-90.
19. Stanworth RD, Kapoor D, Channer KS, Jones TH, Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. *Diabetes Care*, 2009; 32(4): 541-546.
20. Traish AM, Saad F, Guay A, The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. *J Androl.*, 2009; 30(1): 23-32.
21. Dhindsa S, Ghanim H, Batra M, Insulin resistance and inflamation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. *Diabetes Care*, 2016; 39(1): 82-91.
22. Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P., Testosterone concentration in young patients with diabetes. *Diabetes Care*, 2008; 31(10): 2013-2017.
23. Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Vanderschueren D, Huhtaniemi IT, Wu FC, EMAS Group, Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab.*, 2010; 95: 1810-1818.
24. Vari CE, Ősz BE, Perian M, Mărușteri MS, Miklos A, Bosa P, Tero-Vescan A, Do Aromatase Inhibitors Reduce Fertility And Impair Sexual Behaviour In An Androgen Doping Model In Rats?. *Farmacia*, 2017, 65 (3): 336-342.
25. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB, Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab.*, 2002; 87: 589-598.
26. Kim YS, Hong D, Lee DJ, Joo NS, Kim KM, Total testosterone may not decline with ageing in Korean men aged 40 years or older. *Clin Endocrinol (Oxf.)*, 2012; 77: 296-301.
27. Akishita M, Fukai S, Hashimoto M, Kameyama Y, Nomura K, Nakamura T, Ogawa S, Iijima K, Eto M, Ouchi Y, Association of low testosterone with metabolic syndrome and its components in middle-aged Japanese men. *Hypertens Res.*, 2010; 33: 587-591.
28. Auyeung TW, Lee JSW, Kwok T, Ohlsson C, Vandenput L, Leung PC, Woo J, Testosterone but not estradiol level is positively related to muscle strength and physical performance independent of muscle mass: a cross-sectional study in 1489 older men. *Eu J Endocrinol.*, 2011; 164: 811-817.
29. Orwoll ES, Nielson CM, Labrie F, Barrett-Connor E, Cauley JA, Cummings SR, Ensrud K, Karlsson M, Lau E, Leung PC, Lunggren Ö, Mellström D, Patrick AL, Stefanick ML, Nakamura K, Yoshimura N, Zmuda J, Vandenput L, Ohlsson C, The Osteoporotic Fractures in Men (MrOS) Research Group, Evidence for geographical and racial variation in serum sex steroid levels in older men. *J Clin Endocrinol Metab.*, 2010; 95: E151-E160.
30. Van Houten ME, Gooren LJG, Differences in reproductive endocrinology between Asian men and Caucasian men – a literature review. *As J Androl.*, 2000; 2: 13-20.
31. Ohlsson C, Barrett-Connor E, Bhasin S, Orwoll E, Labrie F, Karlsson MK, Ljunggren O, Vandenput L, Mellström D, Tivesten A, High serum testosterone is associated with reduced risk of cardiovascular events in elderly men the MrOS (osteoporotic fractures in men) study in Sweden. *J Am Coll Cardiol.*, 2011; 58: 1674-1681.
32. Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, Ouchi Y, Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. *Atherosclerosis*, 2010; 210: 232-236.

33. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR, Low serum testosterone and mortality in male veterans. *Arch Intern Med.*, 2006; 166: 1660-1665.
34. Ma RC, Tong PC, Testosterone levels and cardio-vascular disease. *Heart*, 2010; 96: 1787-1788.
35. Liao CH, Huang CY, Li HY, Testosterone and sex hormone-binding globulin have significant association with metabolic syndrome in Taiwanese men. *Aging Male*, 2012; 15: 1-6.
36. Dos Santos MR, Sayegh AL, Bacurau AV, Arap MA, Brum PC, Pereira RM, Takayama L, Barretto AC, Negrão CE, Alves MJ, Effect of Exercise Training and Testosterone Replacement on Skeletal Muscle Wasting in Patients With Heart Failure With Testosterone Deficiency. *Mayo Clinic Proc.*, 2016; 91(5): 575-586.
37. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB, Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care*, 2000; 23: 490-494.
38. Sharma R, Oni OA, Gupta K, Sharma M, Sharma R, Singh V, Parashara D, Kamalakar S, Dawn B, Chen G, Ambrose JA, Barua RS, Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation. *Jam Heart Assoc.*, 2017; 6(e004880): 1-8.
39. Yeap BB, Helman AS, Chubb AP, Handelsman DJ, Hankey GJ, Almeida OP, Golledge J, Norman PE, Flicker L, In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *J Clin Endocrinol Metab.*, 2014; 99: E9-18.
40. Janus ED, Wat NMS, Lam KSL, Cockram CS, Siu ST, Liu LJ, Lam TH, The prevalence of diabetes, association with cardiovascular risk factors and implications of diagnostic criteria (ADA 1997 and WHO 1998) in a 1996 community-based population study in Hong Kong Chinese. *Diabet Med.*, 2000; 17: 741-745.
41. Guder G, Frantz S, Bauersachs J, Low circulating androgens and mortality risk in heart failure. *Heart*, 2010; 96: 504-509.
42. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P, Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation*, 2006; 114: 1829-1837.
43. Ikeda Y, Aihara K, Sato T, Akaike M, Yoshizumi M, Suzaki Y, Izawa Y, Fujimura M, Hashizume S, Kato M, Yagi S, Tamaki T, Kawano H, Matsumoto T, Azuma H, Kato S, Matsumoto T, Androgen receptor gene knockout male mice exhibit impaired cardiac growth and exacerbation of angiotensin II-induced cardiac fibrosis. *J Biol Chem.*, 2005; 280: 29661-29666.
44. Ohlander SJ, Varghese B, Pastuszak AW, Erythrocytosis Following Testosterone Therapy. *Sex Med Rev.*, 2017; *in press*.
45. Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, della Monica PL, Bonfigli B, Volpe M, Chierchia SL, Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*, 1999; 99: 1666-1670.
46. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS, Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation*, 2000; 102: 1906-1911.
47. Bhatia V, Chaudhuri A, Tomar R, Dhindsa S, Ghanim H, Dandona P, Low testosterone and high C-reactive protein concentrations predict low hematocrit in type 2 diabetes. *Diabetes Care*, 2006; 29(10): 2289-2294.
48. Beatrice AM, Dutta D, Kumar M, Siddegowda SK, Sinha A, Ray S, Chowdhury S, Testosterone levels and type 2 diabetes in men, current knowlege and clinical implications. *Diab Metab Syndr Obes.*, 2014; 7: 481-486.
49. Ypel M, Ghica MV, Albu Kaya MG, Spoiala A, Radulescu M, Ficai D, Ficai A, Bleotu C, Nitipir C, Multifunctional Materials for Cancer Therapy :From antitumoraal Agents to Innovativ Administration. *Curr Org Chem.*, 2016; 20(28): 2934-2948.
50. Dima M., Timnea O.C., Aspects of muscle activity and medical notions needed by any athlete. Editura Bren Publishing House, Bucharest, 2011, (available in Romanian).