TESTOSTERONE THERAPY, NEW OPPORTUNITIES IN DIABETES MELLITUS

ANCA PANTEA-STOIAN 1#, SILVIU MIREL PIȚURU 2*, RĂZVAN HAINĂROȘIE 3#, LILIANA FLORINA ANDRONACHE 4#, OCTAV GINGHINĂ 5#, CRISTIAN SERAFINCEANU 6,7#

1 “Carol Davila” University OF Medicine and Pharmacy, Faculty of Medicine, Department of Hygiene, 8 Eroii Sanitari Street, Bucharest, Romania
2 “Carol Davila” University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Bucharest, Romania
3 “Carol Davila” University of Medicine and Pharmacy, “Prof. Dr. Dorin Hociotă” Institute of Phonaudiology and Functional ENT Surgery, 21 Mihail Ciocanu Street, Bucharest, Romania
4 “Carol Davila” University of Medicine and Pharmacy, Department of Foreign Languages, 8 Eroii Sanitari Street, Bucharest, Romania
5 “Carol Davila” University of Medicine and Pharmacy, Faculty of Dental Medicine, Department of Surgery, “Sf. Ioan” Clinical Emergency Hospital, 13 Vitan-Bârzești Road, Bucharest, Romania
6-“N. C. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Disease, 5-7 Ion Movilă Street, Bucharest, Romania
7 “Carol Davila” University of Medicine and Pharmacy, Department of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

*corresponding author: piturus@yahoo.com
All authors had equal contribution to this research.

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 puţin o treime dintre pacienţii de sex masculin cu diabet zaharat de tip 2 au asociat o deficienţă a testosteronului. În acest context, oportunitatea pentru medicarea cu testosteron la pacienţii cu hipogonadism şi diabet zaharat de tip 2 devine foarte atrăgătoare dacă luăm în considerare şi efectele sale pleiotropice asupra sindromului metabolic. După cum s-a demonstrat, nivelul scăzut de testosteron este asociat cu o creştere a riscurilor cardio-metabolice, ceea ce duce la creşterea mortalităţii premature. Terapia cu testosteron este relativ sigură, având beneficii potenţiale atât timp cât cazurile sunt atent selectate, iar efectele sale pozitive asupra stării metabolice recomandă această terapie ca o opţiune interesantă la pacienţii cu diabet zaharat şi hipogonadizm 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-
muscular 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
diseases 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 insuline-
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 libido

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% CI 0.81 - 0.99, p = 0.0255) and the 3rd (HR 0.79, 95% CI 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 intima media thickness 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 prothrombotic 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 thromboembolism 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 hypercoagulability [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 cardiovascular 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


