Metabolic Syndrome, Testosterone Deficiency Syndrome and Erectile Dysfunction

Juraj Fillo* and Michaela Levčíkova
Department of Urology, Comenius University, Europe

Abstract
Testosterone plays an important role not only in erectile dysfunction and testosterone deficiency syndrome they may have also influence on the development of metabolic syndrome. In this review are discussed possibilities of action and influence of testosterone on MetS and other comorbidities. Authors also joined own experiences and results.

ABBREVIATIONS
MetS: Metabolic Syndrome; AO: Abdominal Obesity; TDS: Testosterone Deficiency Syndrome; ED: Erectile Dysfunction; TRT: Testosterone Replacement Therapy; TST: Testosterone s

INTRODUCTION
Male sex hormones play an important role not only in erectile dysfunction and testosterone deficiency syndrome (TDS) they may have also influence on the development of metabolic syndrome (MetS). The number of men with abdominal obesity (AO), which constitutes a serious health risk is continuously growing. Men with TDS and MetS can have benefit from treatment with testosterone.

DEFINITION
Testosterone deficiency syndrome is a clinical and biochemical syndrome that results in significant detriment to the quality of life and adversely affects the function of multiple organ systems. TDS is characterized by a decrease in testosterone level (TST) and other hormones DHEAS (dihydroepiandrosteron) and IGF- (insulin growth factor)and is associated with changes in body mass index, obesity, osteoporosis, and sleep and mood disorders [1] shown in Table (I) [2].

Between the age of 40 and 70 years, biologically active free TST in the serum falls by approximately 1.2% per year. There is a similar simultaneous increase in SHBG (sexual hormone binding globulin). In the longitudinal Baltimore Aging Study, 20% of men over 60 years of age, 30% men over 70 year so age and 50% of men over 80 years of age had a low level of total TST. When free, biologically active TST was taken into account, the proportion of hypogonadal men was even higher [3].

Obesity appears to be a driving factor since adipose cells secrete leptin, which results in a decrease in TST level. TST has a wide range of reproductive (sexual) and non-reproductive actions: it preserves bone and muscle mass, it acts on non-sexual mental functioning and it stimulates red blood cell formation.

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. ED is one of the most widespread chronic diseases in men [3]. Currently, it is widely agreed that atherosclerosis vessels of the penis is the cause of organic ED in the majority of cases [4]. Evidence of this can be seen from the fact that the risk factors of atherosclerosis, such as hypertension, diabetes mellitus (DM), dyslipidemia, sedentary lifestyle, obesity and smoking, are common in men with organic ED [3,5]. Moreover, the severity of ED is known to correlate with the number and severity of the above listed disorders, while the combination of these factors raises the risk of developing ED [6].

Metabolic syndrome (MetS) is defined by the presence of at least three of the following: AO, arterial hypertension, lowered HDL (high density lipoprotein), elevated triglycerides, DM or disorder of blood sugar tolerance. Abdominal obesity is defined by WHO (World Health Organisation 1999) and IDF (International Diabetes Federation 2005) for European men: waist circumference over 94 cm and by NCEP (National Cholesterol Education Program 2001) - over 102cm. Recent evidence suggests that TDS is likely to be a fundamental component of MetS [7-9]. There is an inverse relationship between plasma TST and severity of these symptoms [10]. Individuals with MetS carry a twofold increase in relative risk of cardiovascular disease and fivefold increase in relative risk of type 2 DM compared to those without the syndrome [11]. Another very important cause of ED
is a low level of TST. Research has presented convincing evidence that TST has profound effects on tissues of the penis involved in the mechanism of erection and that TST deficiency impairs the anatomical and physiological substrates of erectile capacity [10,12].

Complete urological evaluation: anamnesis, physical examination, including hormonal evaluation (testosterone total, prolactin, follicle stimulating hormone and luteinizing hormone) ultrasonography (USG) and internal evaluation in every patient [13-25]. To assess subjective symptoms related to TDS can be used the Androgen Deficiency Questionnaire (AgingMales' Symptoms AMS Scale) [26], symptoms see also Table (1). To assess erectile function of men, many authors usually used IIEF-5 Questionnaire [27] (0–10 points severe problems, 11–15 medium, 16–21 mild problems). The presence of prostate cancer has to be ruled out by urologist in all patients. (Normal digital rectal examination on prostate and PSA below 4.0 nmol/l.) TST has to be examined two times from 8 to 10:00 a.m. due to the highest level of TST in men in the morning. Algorithm for the diagnosis of TDS is according to the 2001 Consensus Conference of the American Endocrine Society [2,22]. Normal ranges of TST are from 7-28 nmol/l. Examination of free TST is important when results of total TST are in (grey zone) range 7-14 nmol/l. Useful is also bone density in men with low TST. The diagnostics of TDS is in Table (2).

Other disease has to be excluded: as diseases of adenohypofysis, hyperprolactinemia, congenital non-treated hypogonadism (Kallmann’s syd, Klinefelter’s syndrome).

More obese men had more disorders. Therefore is useful divided the men into 5 groups according waist circumference: Grade 0 men with waist circumference (WC) below 94 cm, Grade 1 men with WC from 94 -101 cm, Grade 2 WC 102-109 cm, Grade 3 110-119 cm and Grade 4 over 120 cm. For diagnosis of metabolic syndrome, can be used the classification from Berlin 2005: Berlin modification of criteria NCEP-ATP III [14-16,24,25] Modification of metabolic syndrome for men: Abdominal obesity (waist circumference) >94 cm.

Two from next risk factors:

- Elevated blood pressure >130/85 mmHg
- Triglycerides level TG > 1.7 mmol/l
- HDL-cholesterol level <1.0 mmol/l (men);
- Glucose fasting >6.1 mmol/l

Metabolic syndrome and abdominal obesity

Abdominal obesity has strong influence on metabolic syndrome [25] (Figure 1). No men without AO had MetS. (P=0.000) Out of men with AO 105/198 (53.0%) had diagnosed MetS. There are a significant difference among groups (P=0.000): MetS was diagnosed in 35% men in G1, 51% men in G 2, 84.5% in G 3. and 84% in G 4. (Figure 4). Between G 3 and G 4. there is no significant difference in the number of men with MetS, but when is compared the number of disorders there are differences: in G 3. 17% of men had 5 comorbidities but in G 4. There were nearly twice as many - 32% men had 5 comorbidities.

Table 1: Typical clinical symptoms in older men.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Backache, fractures, decrease in height</td>
</tr>
<tr>
<td>Body composition</td>
<td>Increase in adipose tissue, lipo masty, gynecomasty, decrease in lean tissue</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Muscle atrophy, diminishing strength, neurasthenic weakness</td>
</tr>
<tr>
<td>Skin</td>
<td>Dryness, lack of sebum production, reduced secondary hair growth</td>
</tr>
<tr>
<td>Sexual function</td>
<td>Loss of libido, erectile dysfunction</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Chronic fatigue, neurasthenic weakness</td>
</tr>
<tr>
<td>Vegetative and subjective symptoms</td>
<td>Hyperhidrosis, hot flushes, lethargy, lack of enthusiasm, apathy, lack of self-confidence, anxiety, depression, lack of perspective, sleep disorders.</td>
</tr>
</tbody>
</table>

Table 2: TDS-diagnostics.

<table>
<thead>
<tr>
<th>Age over 40</th>
<th>Decreased libido or ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>From othersigns at least 3:</td>
<td>Lack of energy</td>
</tr>
<tr>
<td>Decline of muscle mass and strength</td>
<td></td>
</tr>
<tr>
<td>Loss of concentration and memory, irritability, depression, loss of enthusiasm and self-confidence</td>
<td></td>
</tr>
<tr>
<td>Decline of cognitive functions</td>
<td></td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td></td>
</tr>
<tr>
<td>Decrease in height</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Metabolic syndrome and abdominal obesity.

Figure 2 Abdominal obesity and ED* (points from IIEF 5 - questionnaire (IIEF 5- International Index of Erectile Functions)).

Erectile dysfunction

Questionnaire for ED are subjective evaluation (IIEF 5): most men with normal erectile function (IIEF 5 over 21) had TST level above 14 nmol/l and most men with the worst ED (0-10 points) had TST level below 7 nmol/l, but this was not significant.
Men without AO: ED had 50% (33% had a mild form, 17% medium and nobody had a severe form of ED). 74.7% of men with AO had together some grade of ED. In group G 1 there were 61% men with ED, in G 2 were 68% in G 3 - 83% and G 4 - 87% men with ED. With growing WC there occurred a more severe form of ED: Figure 2. Differences were significant (P=0.047) [25].

Testosterone deficiency syndrome (TDS). Authors [25] found a strong correlation between TST level and AO. There were more patients with growing AO with a low level of TST. These objective data -TST level - were more significant than a subjective evaluation of men with IIEF 5 and AMS questionnaire. The influence of AO on testosterone level can be seen in Figure (3). Differences were significant (P=0.000). Nearly 89% of men without AO had a TST level over 14nmol/l. Any of these men had TST below 7.0nmol/l. With growing AO there were more men with a low level of TST and only 13% of men in G4 had TST over 14.0nmol/l.AMS questionnaire: men with increasing AO has more and severe problems.

**DISCUSSION**

**Abdominal obesity and TST**

The number of obese people in developed countries is continuously growing. AO seems to be of the same or even higher importance than calculated body mass index BMI [7]. Adipose tissue has suppressive effect on the synthesis of TST. The adipocyte functions as an endocrine cell that produces and secretes adipocytokines /adipokines of which leptin is a prominent member. Leptin receptors are located in Leydig cells and inhibit the TST generated by administration of human chorionic gonadotropin [17]. The examination of patients with ED on TDS becomes important for more reasons. The occurrence of TDS is 38.7 % in men over 45 [18]. In group of patients with AO authors Fillo at al. [25], found 98/198 (49.5%) men with TDS, but in the group of men with AO over 120cm it was 87.1%. The American Urological Association guidelines recognize the importance of screening and treatment of patients with ED. There were [25] a strong correlation between AO, ED, TDS and also MetS.

Mortality and testosterone level: Authors Shores et al. [19], found in a study of male veterans over 40 years without prostate cancer, followed up for a mean of 4.3 years that men with low and fluctuating values (low and normal) serum TST levels, had increased all-cause mortality and shorter survival times compared with men with normal TST levels. In an unadjusted model, low TST levels were associated with an increased mortality risk of 88% greater than that for men with normal TST levels. Khaw et al. [20], found that TST level is in inverse relation to cardiovascular death. Men with TST level above 19.6 nmol/l have 41% lower relative risk of death for all reasons than those who have TST level below 12.5 nmol/l. Multivariate analysis with TST showed that elevation of TST level of 6 nmol/l decreased all reasons of mortality of 14% p <0.001 [20].

Chronic heart failure (CHF) Jankowska et al., 2007 published effect of anabolic hormones for CHF. They found that the age of declining levels of anabolic hormones (AH) - total and free Testosterone, dihydroepiandrosteron (DHEAS) and insulin growth factor (IGF) is associated with higher morbidity and mortality. The authors examined 208 men with CHF average age of 63 years with an ejection fraction of 33% and 366 healthy men. Men with CHF and AH in normal levels had 3 year survival rate of 83%. Men with deficiency of one AH had a 3 year survival rate of 74% , with a deficit of two AH had a 3 year survival rate 55%. Men with deficiency of all AH had a 3 year survival rate 74%. The authors Smith etal., 2006 convincingly demonstrated how blocking testosterone for 12 months changed body P <0.001. Weight increased by 2.5%, muscle mass was reduced by 2.8% and total fat increased by 9.5% [30].

Diabetes mellitus (DM) and insulin resistance. Cross-sectional epidemiological studies have reported a direct correlation between plasma TST and insulin sensitivity. Low TST is associated with an increased risk of type 2 DM in men [21]. In Fillo at al. [22], authors found also in our group of men with TST level below 10nmol/l an increased number of men with DM p= 0.025. Tsai et al. [23], show that all these three factors - obesity, insulin resistance or hypogonadism can trigger/start MetS. Authors Smith et al., 2006 convincingly show how blocking testosterone is reduced insulin sensitivity and glucose level rises [30,31].

Osteoporosis Testosterone deficiency causes reduced bone mineralization, resulting in osteopenia or osteoporosis. Androgens have an anabolic effect. However 17beta estradiol is more important to bone metabolism in men than.
TST. Because the enzyme aromatase is present in osteoblasts, these are capable of converting androgens to estrogens [32]. Studies of the effect of TRT on bone metabolism in older men show a reduction in bone loss and reduced excretion of bone degradation parameters (hydroxyproline, pyridinoline) [33]. Four study conducted over periods of between 12 and 36 months evaluated bone density and revealed an increase in spinal bone density [34]. Testosterone has strong anabolic effect on bones as was proved also in our study. (up to now our unpublished data).

Sufficient level of TST There is still not consent which level of TST is sufficient for proper metabolism. Fillo et al. [22] found that men with TST over 14 nmol/l had the smallest number of DM, hypertension and best results of HDL and triglycerides. There was significant difference between patients with TST below 10nmol/l and over 14nmol/l in DM, hypertension, HDL and triglycerides (TG) level. They found that there were differences also between groups of men with TST between 10-14 and over 14nmol/l in level of HDL and triglycerides. These findings suggest similar to [20] that sufficient level of total TST should be minimum 10nmol/l but better over 14nmol/l.

Treatment of TDS

TRT for restoring normal level of TST 14-28nmol/l, not to reach supraphysiology level. TRT has to be long lasting due to men alone are not able to produced enough TST. Also important is reach a stable level of TST. Most suitable for these reasons are long lasting 3 months injection with 1000mg TST. At the beginning of TRT after the first injection, the second is after 6 weeks to reach a stable level of TST than every three months. Four injections per year are well accepted by patients. Pills with TST must be taken every 6 hours. In this case it is important to check liver function. Other possibilities of administrations are: sublingual, transdermal, buccal or subdermal depots.

When level of TST is restored started its anabolic effect on all listed disorders above. Best example which can be verified is improving bone density in men on TRT.

Complications of TRT

Polyglobulia. This is not true complication. Anabolic effect of TST on bone marrow is production of red blood cells. On TRT started production of red blood cells (RBC) and continue beside level of RBC became normal. In this case has to be extended interval of injections with TST from 12 to 14 weeks, or lower dose of pills.

There was proved that TST not supported prostate cancer. Only small number of pts has temporarily rising of PSA. PSA usually falls without discontinuation of TRT.

Obstruction sleep apnoea(OSA): There is no consistent evidence correlating TRT with OSA. There is also no evidence that TRT can result in the onset or worsening of the condition (European Urology Guidelines 2016 [29]).

CONCLUSIONS AND RECOMMENDATIONS

Men with MetS carry a twofold increase in relative risk of cardiovascular disease and fivefold increase in relative risk of type 2 DM compared to those without the syndrome [11]. The distribution of men according to the degree of abdominal obesity brought simplifying and speeding up diagnosis of TDS. There are significant differences between men with and without AO. Men with AO had a higher number of ED 74.7%, TDS 49.0% and MetS 53%. [25]. TRT may improve symptoms, but many hypogonadal men have a chronic illness and are obese: weight reduction, lifestyle modification and good treatment of comorbidities is more important than just TRT. TRT can improve body composition, bone mineralisation, signs of the MetS and male sexual problems. A reduction in BMI and AO improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT [31].

Early diagnosis of men with ED, TDS and MetS and treatment these men with TRT restore normal range of TST and can significantly improve all symptoms in male osteoporosis.

REFERENCES

2. The Endocrine Society: 2nd annual consensus meeting on andropause. J Clin Endocrinol Metab. 2004; 188: 112-123.
Massachusetts male aging study. J Clin Endocrinol Metab. 2002; 87: 589-598.


