Corona, Giovanni; Maggi, Mario

PATIENTS WITH TESTOSTERONE DEFICIENCY SYNDROME AND TYPE 2 DIABETES

Archivos Españoles de Urología, vol. 66, núm. 7, septiembre, 2013, pp. 711-722

Editorial Iniestares S.A.
Madrid, España

Available in: http://www.redalyc.org/articulo.oa?id=181031085013
PATIENTS WITH TESTOSTERONE DEFICIENCY SYNDROME AND TYPE 2 DIABETES

Giovanni Corona¹ and Mario Maggi².

¹Endocrinology Unit. Medical Department. Azienda USL Bologna. Maggiore-Bellaria Hospital. Bologna. Italy.

Summary.- The prevalence of diabetes mellitus (DM) is increasing worldwide for all ages due to population growth, aging, and increased prevalence of obesity and physical inactivity. Sexual dysfunction and in particular erectile dysfunction (ED) are frequent complications of DM. In patients with DM, ED can be considered as a useful sign of silent myocardial ischemia. A large body of evidence also supports a strong association between DM, cardiovascular risk (CV) and testosterone deficiency syndrome. Despite this evidence, the screening of ED and hypogonadism in the diabetic population remains poorly implemented. In addition, data regarding the role of testosterone replacement therapy (TRT) for glycometabolic control and CV risk remains contradictory. In the present paper we have reviewed the available evidence and based our discussion on data derived from a specific clinical case.

Hypogonadism is frequently observed in subjects with type 2 DM (T2DM) and especially those complaining of ED. Obesity and insulin-resistance are probably the most important pathogenetic factors involved, and, according to the current guidelines, subjects with T2DM should be screened for hypogonadism. TRT is the first line option in hypogonadal subjects with ED, however, the possible role of TRT in improving glycometabolic control and CV outcomes needs to be confirmed through longer and larger studies.

Keywords: Testosterone. Hypogonadism. Diabetes. Erectile dysfunction. Obesity.


CORRESPONDENCIA

Mario Maggi
Sexual Medicine and Andrology Unit, Department of Biomedical, Clinical and Experimental Sciences
University of Florence
Florence Viale Pieraccini 6, 50139 Florence, (Italy)
m.maggi@dfc.unifi.it
G. Corona and M. Maggi.

**INTRODUCTION**

Type 2 diabetes (T2DM) is a complex metabolic disorder characterized by hyperglycemia, relative deficiency of insulin secretion and a reduced response of target tissues to insulin (insulin resistance) strictly associated with overweight and obesity. The dramatic worldwide increase in the prevalence of T2DM is posing a massive health problem in both developed and developing countries (1-3). In particular, T2DM was ranked third among the ten most prevalent diagnosed diseases in a representative US population of men older than 50 years of age (1). The prevalence of T2DM for all age-groups worldwide was estimated to be 2.8% in 2000, with a projection of 4.4% in 2030 due to population growth, aging, and increased prevalence of obesity and physical inactivity (2). Similar data have been reported in the European population (4-5). Interestingly, we recently demonstrated that in a large series of patients seeking medical care for ED, not only diabetes, but also milder glucose abnormalities, such as impaired fasting glucose, harbor the risk of more severe ED, reduced penile blood flow and overt hypogonadism (22).

A large body of evidence has also emphasized the concept that ED can be considered as a useful sign for the screening of silent myocardial ischemia in diabetic subjects (23-24). In addition, recent data support a possible association between hypogonadism and increased mortality (25-26).

Despite this evidence, the screening of ED and hypogonadism in the diabetic population remains poorly investigated (16, 27-28). In addition, data regarding the role of testosterone replacement therapy (TRT), for glycometabolic control and CV risk, remains contradictory.

The aim of the present review is to discuss all the impacts of hypogonadism in subjects with DM and the possible role of testosterone replacement therapy in these subjects.

**CLINICAL SCENARIO-THE REAL STORY**

**Personal background**

A 52-year-old man presented for ED. He was a foundry owner and he was very happy but stressed from his job. He was a heavy smoker in the past and only rarely consumed alcohol. He had a normal pubertal development. His family history was positive for T2DM (mother), stroke (mother), and hypertension (father). He has had hypertension since 1980 and T2DM since 1985.
Tabla I. Characteristics of the patients. BMI= body mass index, SBP= systolic blood pressure; DBP= diastolic blood pressure, HDL= high density lipoprotein, LH= luteinizing hormone, PSV= peak systolic velocity; ED= erectile dysfunction. IIEF= international index of erectile function.

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>130</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>185</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>38.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>(&lt; 25)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80</td>
</tr>
<tr>
<td>Right testis volume (ml)</td>
<td>11</td>
</tr>
<tr>
<td>Left testis volume (ml)</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia (mg/dl)</td>
<td>258</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11.1%</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>240</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>245</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>38</td>
</tr>
<tr>
<td>TSH (U/L)</td>
<td>1.58</td>
</tr>
<tr>
<td>FSH (U/L)</td>
<td>6.1</td>
</tr>
<tr>
<td>LH (U/L)</td>
<td>5.1</td>
</tr>
<tr>
<td>Total testosterone (nmol/L)</td>
<td>7.54</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>14</td>
</tr>
<tr>
<td>Calculated free testosterone (pmol)</td>
<td>201</td>
</tr>
<tr>
<td>Prolactin (mU/L)</td>
<td>88</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Instrumental parameters</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left internal carotid artery</td>
<td>Stenosis 40%</td>
</tr>
<tr>
<td>Right internal carotid artery</td>
<td>Stenosis 35%</td>
</tr>
<tr>
<td>Dynamic PSV (cm/s)</td>
<td>24</td>
</tr>
<tr>
<td>SIEDY scale score</td>
<td>(&gt; 25)</td>
</tr>
<tr>
<td>Scale 1 (organic domain of ED)</td>
<td>(&lt;3)</td>
</tr>
<tr>
<td>Scale 2 (relational domain of ED)</td>
<td>(&lt;2)</td>
</tr>
<tr>
<td>Scale 3 (intrapsychic domain of ED)</td>
<td>(&lt;3)</td>
</tr>
<tr>
<td>Androtest score</td>
<td>14</td>
</tr>
<tr>
<td>IIEF-5 score</td>
<td>10</td>
</tr>
</tbody>
</table>

Normal values:
- Weight: < 25 kg
- Height: > 102 cm
- SBP: > 130 mmHg
- DBP: < 85 mmHg
- Right testis volume: > 12 ml
- Left testis volume: > 12 ml
- Glycemia: 60-110 mg/dl
- HbA1c: < 6.5%
- Total cholesterol: 70-220 mg/dl
- Triglycerides: < 180 mg/dl
- HDL cholesterol: 40-70 mg/dl
- TSH: 0.4-4.4 U/L
- FSH: 5-25 U/L
- LH: 5-20 U/L
- Total testosterone: 10-30 nmol/L
- SHBG: 12.9-61.7 nmol/L
- Calculated free testosterone: > 225 pmol
- Prolactin: 60-422 mU/L
- PSA: < 4 ng/ml
- Stenosis: > 25%
- SIEDY scale score: < 3
- Androtest score: < 8
- IIEF-5 score: > 21
Current therapy was based on insulin, metformin, statin, acetylsalicylic acid and angiotensin II receptor blocker.

His partner was 48 years old, with a good relationship lasting more than 20 years. The partner had quite good general health. She reported having normal libido, orgasmic functioning and a normal menstrual cycle. They did not have children at the time.

The patient’s problem deals with an erection insufficient for penetration in 100% of occasions. The problem started more than 2 years ago, gradually. He also reported severely impaired sleep related erections and a mild reduction of sexual desire. In addition, he complained of a reduced ejaculate volume whereas orgasmic functioning and ejaculatory timing were normal. The same problems were present during autoerotism and he reported a frequency of intercourse of 1-2 times/week.

**Relevant clinical data**

Physical examination revealed central obesity (body mass index 38.1 Kg/m$^2$), waist circumference 127 cm with slightly reduced testicular volume (bilateral 11 cc) and reduced prostate volume at digital rectal examination (DRE). The penis was normal and no clinical suspicion of varicocele was detected. Blood pressure was normal 130/80 mmHg, but physical examination showed the presence of bilateral carotid murmur.

The patient was interviewed with SIEDY structured interview, a 13-item structured interview made-up of 3 scales dealing with organic, relational and intrapsychic factors involved in the pathogenesis of ED, which showed a major contribution of organic factors (29-30). In addition, he was also interviewed with ANDROTEST, a 12-item interview specifically developed and validated for the screening of hypogonadism in patients seeking medical care for sexual dysfunction, where a high score indicates the presence of male hypogonadism (31). The patient was also invited to complete the international index of erectile function for the quantification of ED severity (32; see also Table I).

**Complementary tests**

According to the current guidelines, the patient was prescribed glycometabolic and hormonal examinations as well and a treadmill-test (33). In particular, the treadmill-test was prescribed according to the 3rd Princeton Consensus panel which suggests second line cardiological evaluation in patients at intermediate risk such as in this case (34). In addition, a penile doppler ultrasound (PDU) and a carotid doppler ultrasound were also prescribed to check his vascular status. Biochemical and hormonal exams are reported in Table I.

They essentially show the presence of overt hypogonadism and not sufficiently compensated DM. It is important to emphasize that among the different symptoms, sexual symptoms represent the most specific symptoms associated with testosterone deficiency syndrome (TDS). In fact, recent data from the European Male Aging Study (EMAS; 35) recognized that a triad of sexual symptoms (low libido and reduced spontaneous and sex-related erections) is the only syndrome associated with decreased testosterone levels, whereas other proposed hypogonadal symptoms did not segregate with androgen deficiency. The present patient had all three of these symptoms as well as a high ANDROTEST score. Other suspected clinical signs of hypogonadism in this specific case were represented by semen ejaculate volume and prostate volume. In addition, the presence of DM and central obesity represent other clinical conditions at high risk for TDS. Accordingly, current guidelines suggest to rule out hypogonadism in the presence of T2DM and obesity (21; see below).

The treadmill test was negative but penile PDU was indicative of bilateral penile atherosclerosis.
Patients with testosterone deficiency syndrome and type 2 diabetes whereas carotid doppler ultrasound showed the presence of non-emodinamic bilateral carotid stenosis (Table I).

Treatment and follow up
Testosterone replacement therapy (TRT) was prescribed and a 3 month check-up scheduled. Androgens modulate the expression of both nitric oxide synthases and phosphodiesterase type 5 (PDE5) and therefore normal androgenization is a prerequisite for proper functioning of PDE5 inhibitors. In other words, TRT should be considered the first line of treatment in ED patients with hypogonadism. Patients treated with TRT should be monitored at 3–6 months during the first year, and at least annually thereafter. At each visit a careful clinical and andrological evaluation, including DRE, is mandatory. Biochemical assessment must include the evaluation of PSA and hematocrit.

The patient did not attend the visit since he was hospitalized for a mild stroke 2 months after the last visit. The neurologist suggested interrupting the TRT since it could exacerbate a stroke.

Evolution
The relationship between cardiovascular (CV) risk and hypogonadism has not been completely clarified [13, 38]. However, it is important to recognize that three meta-analyses found no significant difference between the testosterone and placebo groups for all CV events, nor for each type of event (39-41; see below). Moreover, increased androgen levels have been shown to improve metabolic control and CV outcomes in patients with T2DM [20; see below].

This patient in particular totally recovered from the stroke in a month. He was informed on the available evidence regarding TRT and CV disease and he eventually decided to start TRT again. After three months improvement of metabolic control (HbA1c 7.8%) but sexual problems were still present. At this point PDE5i was introduced with a successful outcome. As previously mentioned, androgens modulate the expression of PDE5 [42]. Several uncontrolled and randomized placebo-controlled studies have confirmed that hypogonadism hinders the effects of PDE5-Is on erectile function [36]. Accordingly, available evidence suggests that the combination of testosterone and PDE5Is is able to improve the overall efficacy from 34 to 100% [36, 42].

Table II. Individual randomized controlled studies evaluating the impact of testosterone replacement therapy (TRT) in type 2 diabetic subjects. ID/C: Investigational Drug/Comparator. TU= testosterone undecanoate. TT= total testosterone (T).

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Location</th>
<th># patients (ID/C)</th>
<th>Hypogonadism cut off</th>
<th>Trial duration (weeks)</th>
<th>Drugs</th>
<th>Comparator</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyanov et al. 2004</td>
<td>Sofia, Bulgaria</td>
<td>24/24</td>
<td>TT &lt;15 nM</td>
<td>12</td>
<td>O-TU 120 mg daily</td>
<td>No TRT group</td>
<td>58.0</td>
</tr>
<tr>
<td>Correales et al. 2004</td>
<td>Salamanca, Spain</td>
<td>10</td>
<td>TT &lt;12 nM</td>
<td>12</td>
<td>T-enanthate 150 mg/2 weeks</td>
<td>No comparator</td>
<td>63.8</td>
</tr>
<tr>
<td>Kapoor et al. 2006</td>
<td>Sheffield, UK</td>
<td>12/12</td>
<td>TT &lt;12 nM</td>
<td>12</td>
<td>i.m T 200 mg/2 weeks</td>
<td>Placebo</td>
<td>64.0</td>
</tr>
<tr>
<td>Heufelder et al. 2009</td>
<td>Munich, Germany</td>
<td>16/16</td>
<td>TT &lt;225 pM</td>
<td>52</td>
<td>T gel 1% 50 mg/daily</td>
<td>Placebo</td>
<td>56.6</td>
</tr>
<tr>
<td>Gopal et al. 2010</td>
<td>Mumbai, India</td>
<td>11/11</td>
<td>TT &lt;11 nM</td>
<td>52</td>
<td>i.m T 60 mg/2 weeks</td>
<td>Placebo</td>
<td>44.2</td>
</tr>
<tr>
<td>Jones et al. 2011</td>
<td>Multicenter</td>
<td>64/65</td>
<td>TT</td>
<td>52</td>
<td>T gel 2% Daily</td>
<td>Placebo</td>
<td>60.0</td>
</tr>
</tbody>
</table>
Pathogenesis of diabetes mellitus associated hypogonadism

The pathogenesis of DM-associated hypogonadism is complex and has not been fully elucidated (42-43). First of all, it is important to recognize that while the association between T2DM and reduced testosterone levels is well recognized and supported by two independent meta-analyses (19-20), studies on men with type 1 diabetes (T1DM) have shown conflicting results (44-47). Figure 1 shows the prevalence of hypogonadism in a consecutive series of 3451 subjects (mean age 51.3±13.2 years old) attending our Unit seeking medical care for sexual dysfunction between 2000 and 2011. Independently of the criteria used for the definition of hypogonadism, type 2 (n=675; 19.6% of the whole population) but not type 1 DM subjects (n=60; 1.7% of the whole population) have a significantly higher prevalence of hypogonadism when compared to the rest of the sample. The latter was confirmed even after the adjustment for age and BMI. Interestingly, the prevalence of hypogonadism observed in our population is slightly higher than that reported in the general diabetic population. In particular, Anderson et al., (48) in a large series of 6457 male patients aged 18-80 years with T2DM, demonstrated that 4.4% of them were clearly hypogonadal with a serum total testosterone of less than 8.0 nmol/l. For borderline hypogonadism (serum total testosterone 8-11.99nmol/l) the proportion of T2DM men rose to 32.1%. These differences are not surprising since subjects with ED represent a population saturated with hypogonadism as previously reported (12, 20).

Obesity and insulin resistance probably represent the most important factors involved in the pathogenesis of diabetes-mellitus induced hypogonadism (Figure 2). The androgen receptors are highly expressed in visceral fat and negatively regulate the differentiation of preadipocytes into mature adipocytes (49). Androgens decrease fat mass by regulating the differentiation of mesenchymal stem cells to adipocytes (49). Furthermore, the increased aromatization of testosterone to estradiol observed in obese men can induce a negative feedback on both the hypothalamus and pituitary leading to the development of a hypogonadotropic hypogonadism (7-8, 50-51). Accordingly, Biswas et al., (47) recently demonstrated that the role of obesity (strictly associated with T2DM) is similar in type 1 diabetes and in the healthy population.

Insulin itself is capable of stimulating testosterone production and, simultaneously, of inhibiting sex-hormone-binding globulin (SHBG) concentration (52). In addition, animal models of insulin-deficient diabetes are characterized by the
presence of hypogonatropic hypogonadism (53-54) partially reverted by insulin administration suggesting a possible role of insulin in regulating hypothalamus GnRH synthesis. Hence, both the presence of central and peripheral mechanisms are presumed to be involved in the pathogenesis of hypogonadism associated with diabetes.

The state of glycometabolic control might represent another crucial factor. Our data show that the risk of hypogonadism increases as a function of HbA1c tertiles reaching its maximum in the higher tertile (HbA1c>8%). It should be recognized, however, that previous studies taking glycemic control into account in the evaluation of T2DM related hypogonadism have reported conflicting results, showing either an association (55-57) or a lack of association (46; 58-60) between glycemic control and testosterone levels.

According to our data the use of statins was associated with a 4-fold increased risk of hypogonadism. Statins operate by inhibiting the enzyme 3-hydroxy-3-methylglutaryl Coenzyme A reductase, the rate-limiting enzyme in cholesterol formation, and therefore steroid, synthesis (61). The idea that the inhibition of cholesterol synthesis may interfere with testosterone production has been examined, with mixed results (61). We previously reported a negative association between statin therapy and both total and free testosterone levels, independently of the type of statin and the dosage used (61). Hence the use of statins should be considered a possible confounding factor for the evaluation of testosterone levels even in patients with T2DM.

Besides all the aforementioned factors, our data suggests that even the impairment of the relational factor underlying ED as detected by SIEDY Scale 2 score significantly increased the risk of hypogonadism in this specific population. We previously reported that in subjects consulting for sexual dysfunction, deterioration of the couple’s relationship may be associated with impairment in sexual activity, which, in turn, can lead to a mild hypogonadism (62-64). Accordingly, over the last few years, the Jannini group has produced further evidence substantiating the hypothesis that sexual inertia resets the reproductive axis to a lower activity, somehow inducing a secondary hypogonadism, characterized by reduced LH bioactivity (65-67).

**TRT and glycometabolic control**

So far, only five studies have been published on this topic (see also Table II). In 2003 Boyanov et al. (56) reported the effect of oral testosterone undecanoate (TU, 120mg/daily) in 24 T2DM subjects in an open-label comparison with 24 control subjects who did not receive TRT. After 12 weeks, TU significantly improved metabolic control (fasting and post-prandial glycaemia and mean HbA1c), reducing also visceral adiposity. In a subsequent study, Corrales et al. (68) evaluated the impact of TRT on overall glycaemic indexes in an underpowered pilot study involving only 10 T2DM subjects without demonstrating any significant improvement of glycometabolic control. In 2006 Kapoor et al., (57) published the first double-blind placebo-controlled randomized controlled study (RCT) studying that TRT determined an improvement of glycometabolic control (fasting glycemia and HbA1c) as well as insulin sensitivity (HOMA index) in 16 patients with T2DM. They also reported a reduction in visceral adiposity (waist circumference and waist/hip ratio) and in total cholesterol. Furthermore, the same authors, in a subsequent study involving the same series of subjects, demonstrated that TRT is associated with a reduction of leptin and adiponectin levels (69). Furthermore, in 2009 Hufeelder et al. (70), in a small randomized controlled study involving 16 subjects with newly diagnosed T2DM and metabolic syndrome (MetS), demonstrated that the combination of TRT and lifestyle interventions led to greater therapeutic improvements of glycemic control and even reversed the MetS after 52 weeks of treatment. More recently, Gopal et al (71) in another double blind placebo controlled RCT involving 22 men with T2DM did not find any statistical difference between TRT or placebo in HOMA index and glycometabolic control after 12 weeks. Finally, in 2011, Jones et al (72) published data on TIMES 2, the largest placebo-controlled study evaluating the effect of T gel 2% over 12 months in 220 hypogonadal men with T2DM and/or MetS. At the end of the study, sub-analysis on T2DM showed that TRT was able to improve HOMA index, HbA1c and waist circumference. Interestingly, after a meta-analysis of some of the available evidence, we previously reported that in patients with T2DM, TRT was associated with a significant reduction in fasting plasma glucose, HbA1c, fat mass, and triglycerides (20).

Hence, although only limited information is available, present data suggest that TRT in T2DM is safe and could improve glycometabolic control.

**Testosterone and CV disease**

Despite the strong association between reduced testosterone levels and T2DM, the role of testosterone in the pathogenesis of male CVD is conflicting. In particular, while the majority of the studies performed in community dwelling men did
not report any associations between cardiovascular (CV) risk and testosterone levels, some Authors have suggested a link between low testosterone and an increased risk of CV lethality (see ref. 25-26 in for review). In a consecutive series of more than 1600 men attending our unit for ED we found that low testosterone, even in the overt hypogonadal range (below 8 nmol/L), was not predictive of CV morbidity, while it was predictive of CV mortality (73). Similar results have been reported in specific sub-populations such as patients with hypopituitarism (74), Klünefelter’s syndrome (75), mental retardation (76), veterans (77), or men with at least one CV factor (78). Whether or not low testosterone plays a direct pathogenetic role in increasing CV mortality is still a matter of speculation. The possibility that low testosterone does not play a causal role but represents only an indicator underlying illness or associated morbidities cannot be excluded at all. Accordingly, two independent meta-analyses have documented that low endogenous testosterone levels are associated with an increased risk of all-cause and CVD death, but not with CVD incidence (25-26). Furthermore, meta-analyzing cross sectional data on testosterone and CVD we found that subjects with CVD have significantly lower testosterone levels but these differences are attenuated by the presence of several associated morbidities, including diabetes, obesity and hypertension (25). Taken together, these results suggest that low testosterone may be considered as a marker of poor general health status, negatively affecting prognosis, rather than a specific CV risk factor (25,38). In line with the latter hypothesis, we recently found that body mass index (BMI) played a crucial role in the stratification of hypogonadism-associated CV risk. In a retrospective analysis of a large series of subjects with sexual dysfunction, we showed that testosterone levels were inversely related to CV risk (79). However, when obese subjects were compared to the rest of the sample, the association between testosterone and CV risk was confirmed only in overweight and normal weight subjects (79). Similarly, we observed a positive association between forthcoming major adverse cardiovascular events (MACE) and reduced testosterone levels in normal weight and overweight subjects, which was lost when obese (BMI > 30 Kg/m²) patients were considered (80). Hence, while reduced testosterone might contribute to CVD the reverse is also possible. It can be speculated that low testosterone during chronic diseases represents a protective mechanism, which could turn off testosterone-dependent functions (such as reproduction and physical labor) that are not desirable when the physical condition is ailing. Similar adaptive mechanisms have been previously described for other hormonal axes (80). A typical pattern of altered thyroid hormone metabolism, characterized by low T3 circulating levels (low T3 syndrome), has been reported in patients with different chronic illnesses, including CVD.

**TRT and CVD**

Some clinical and animal evidence showed that testosterone exerts a favorable effect upon vascular reactivity, inflammation, cytokine production, and adhesion molecule expressions, as well as on serum lipid concentration and haemostatic factors suggesting a favorable effect of TRT on CV outcomes (see for review 5-26, 81). A recent RCT study using a high dose transdermal T (100 mg of a 1% gel) on more than 200 hypogonadal (total testosterone below 12 nmol/L) frail, elderly men showed a high rate of testosterone-associated CV adverse events (82). These data raised enough concern to warrant termination of this study. These same authors recognized that the data about the safety of TRT is limited by several factors, including that CV events were not a planned primary or secondary outcome measure and that the actual number of the adverse events was relatively small (23 vs. 5 respectively for treatment and placebo arms) (91). In contrast to this study, three other meta-analyses found no significant difference between testosterone and placebo groups for all CV events, nor for each type of event, except for an increase in hematocrit over 50%, which was significantly more common in the testosterone group (39-41). In addition, meta-analysis of specific data from studies involving subjects with CVD showed that TRT was effective in men with chronic stable angina, as subjects had a higher angina-free exercise tolerance than placebo-treated controls.

**Message and Recommendation**

Hypogonadism is frequently observed in subjects with T2DM and especially those complaining of ED. According to the current guidelines subjects with T2DM should be screened for hypogonadism. TRT is the first line option in hypogonadal subjects with ED. The possible role of TRT in improving glycometabolic control and CV outcomes needs to be confirmed through longer and larger studies.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)


