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ORIGINAL ARTICLE

Male Hypogonadism and Type 2 diabetes Mellitus

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***Abstract:** As prevalence of diabetes mellitus is rising high, it is also not unexpected that associated complications are also going to take new dimensions. Male hypogonadism is defined as the failure of the testes to produce androgen, sperm, or both. Low serum testosterone is almost always associated with impaired sperm production. However, isolated impairment of sperm production or function is also possible in the background of normal serum testosterone. Clinical manifestations of testosterone deficiency depend on the age at which androgen deficiency becomes apparent. Fetal androgen deficiency may manifest with variable degree of genital ambiguity.*

Prepubertal onset of androgen deficiency is characterized by eunuchoidism. Limbs are longer relative to height because of failure of epiphyseal closure in the background of low serum testosterone. Normally, testosterone is converted into estrogen which promotes epiphyseal closure in both sexes around puberty. Arm span exceeds height by 5 cm. Infantile genitalia along with high pitched voice in an adult male is also indicator of prepubertal androgen deficiency.

Introduction

On the other hand, postpubertal onset of androgen deficiency will have normal body proportion along with normal voice. They usually present with diminished libido along with reduced spontaneous and evoked erections. Usually, they have diminished energy, decreased motivation,depressed mood with increased sleepiness, irritation and social aggression. Lean body mass and muscle mass are decreased along with increased fat masswhich lead to reduced exercise capacity. Reduced sebum secretion may lead to development of fine facial wrinkling at lateral canthus and angle of mouth.

Long standing testosterone deficiency may present with small testicular size. But, in most of the cases testicular size is normal. Bone health is also impaired increasing the chance of osteoporosis and fragility fracture.

Serum testosterone level reflects the integrity of the Hypothalamic Pituitary Gonadal axis. Primary hypogonadism is caused by defects in testes. Secondary hypogonadism is because of either hypothalamic or pituitary defect. Combined defects in both primary and secondary level have also been noted.

The age-related decline in testosterone levels[1, 2] results from defects in both testicular and hypothalamic-pituitary function. Average decline in serum testosterone levels with aging in men is reported around 1–2% per year.[1,2] So, only a subset of aging men will have levels clearly below the lower limit of the normal range for healthy, young subjects.[3]

Type 2 diabetes (T2DM) is associated with low total testosterone in different cross-sectional studies. Total T concentrations are determined to a large extent by circulating sex hormone-binding globulin (SHBG) concentrations. In the blood of normal men, 44% of total T is bound to SHBG, 2% is unbound [free T], and 54% circulates bound to albumin and other proteins.[4] Albumin-bound T can freely disassociate in capillaries. So, all the non-SHBG-bound T (also called BT) is therefore available for tissue uptake.[5] Circulating SHBG concentrations depend on a number of factors. SHBG levels decrease in obesity and increase

with aging. Type 2 diabetics have even lower SHBG levels compared with age- and BMI matched nondiabetics[6].

Barrett-Connor [7] in the Rancho Bernardo Study found that the 44 elderly men (age range: 53–88,mean: 72 yr) with T2DM had lower free (4.96 nmol/L compared with 5.58 nmol/L) and total Testosterone (14.7 nmol/L compared with 17.4 nmol/L) levels than age- and BMI-matched 88 nondiabetics.Lower levels of total T was also noticed in men with impaired glucosetolerance group in the Rancho Bernardo study.[8] Total testosterone and fasting plasma glucose were inversely associated in men (P = 0.0001).[8]

Another case control study observed lower total T levels in 16 European and 77 Melanesian men with T2DM compared with an equal number of controls.[9]

Andersson *et al.*[10] reported lower total T and SHBG levels in 46 diabetics compared with 11 healthy men of similar BMI and age.

In Iran,[11] total testosterone (TT) and SHBG were measured in 247 diabetic men aged >30 years who had symptoms of androgen deficiency, according to ADAMs questionnaire. Free and bioavailable testosterone were calculated by electronic calculator. According to TT and cBT, overt hypogonadism was observed in (total testosterone ≤8 nmol/L or calculated bioavailable testosterone ≤2.5 nmol/L) 7.4% and 61.6% of men, respectively[11] and borderline hypogonadism was found (as TT 8–12 nmol/L or cBT 2.5-4nmol/l) in 9.9% and 36%, respectively. Hypogonadism (TT ≤12 nmol/l) was not correlated with obesity, smoking, age, duration of diabetes, blood pressure, and HbA1c.[11]

Kapoor *et al.*[12] found overt hypogonadism in 17% of men with total testosterone <8 nmol/L and 14% with bioavailable testosterone <2.5 nmol/L in a cross-sectional study of 355 type 2 diabetic men aged more than 30 years. Borderline hypogonadism (defined as the presence of symptoms and total testosterone of 8–12 nmol/L or bioavailable testosterone of 2.5–4 nmol/L) was found in 25% of men.

Sandeep Dhindsa *et al.*[13] observed 33% of patients were hypogonadal in their cohort.

Metabolic syndrome, insulin resistance, and visceral obesity have all been correlated with low SHBG and low total T levels in men in different studies. Tsai *et al.*[14] found that free and bioavailable testosterone correlated inversely with body fat measurements.

Sex hormone-binding globulin is diminished with obesity leading to low testosterone level. However, because of low SHBG, bioavailable testosterone level may remain unchanged. Androgen is converted in adipose tissue to estrogen. This may also contribute to low testosterone levels.

Dhindsa *et al.*[13] found that luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were significantly lower in the hypogonadal group compared with patients with normal free testosterone (FT) levels. They concluded that hypogonadotropic hypogonadism occurs commonly in T2DM. If it is believed that the low total T in obesity is caused by lowSHBG concentrations, then FT levels should not be low in massively obese males. But, it is not the fact. Obesity is associated with increased plasma levels of TNFα, IL-6, C-reactive protein, and adhesion molecules.[15] TNF α and IL-1 can reduce hypothalamic GnRH and LH secretion.[16]

Endocrine Society [17] recognized high prevalence of low testosterone level in diabetes and suggested assessment of the Hypothalamic Pituitary Gonadal axis in different conditions including diabetes.

Over the last decade concepts are developing that male hypogonadism and testosterone deficiency can precipitate insulin resistance and subsequent T2DM.

Nelly Pitteloud *et al*[18] found low serum testosterone level was associated with an adverse metabolic profile. It was noticed that subjects with hypogonadal testosterone levels (n = 10) had a BMI >25 kg/m^2 and a three-fold higher prevalence of the metabolic syndrome than their eugonadal counterparts (n = 50). It was consistent after adjusting for age and SHBG but not BMI.[18] Sex hormone-binding globulin is supposed to link between testosterone and insulin sensitivity.

The relationship between androgens and BMI is likely bidirectional. Morbid obesity has negative effects on the hypothalamic-pituitary-gonadal axis in men. On the other hand, low testosterone levels predispose to central[19] and visceral adiposity. Visceral obesity may lead to dysregulation of fatty acid metabolism which in turn promotes insulin resistance.[20]

Agarwal S *et al.* found that testosterone suppression with GnRH agonist in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia in 2003.[21] Smith JC *et al.*[22] reported same effects of induced hypogonadism on arterial stiffness, body composition and metabolic parameters in males with prostate cancer in 2001.

Kapoor *et al.*[23] reported in their study that testosterone treatment reduced insulin resistance and improved glycaemic control in hypogonadal men with T2DM.

Insulin resistance is improved chiefly through reduction in visceral adiposity following testosterone treatment. In the background of excess visceral fat, liver is exposed to higher amounts of free fatty acids. It leads to hepatic and eventually systemic insulin resistance.[24]

An anti-inflammatory effect of testosterone replacement therapy has been established. Testosterone reduces TNF a, Il-1b levels and increases anti-inflammatory cytokineIL-10 levels.[25]

So, insulin resistance and testosterone deficiency walk hand in hand. One can enhance the other. Improvement of one side with help of available protocol may help in betterment of another side. But, recent adverse report, published on January 29th, 2014 in *PLoS One* online journal done by William D Finkle et al, of testosterone therapy in

elderly hypogonadal persons with cardiovascular risk also raises a question mark regarding routine use of testosterone in this group of persons.The increased risk was found in men younger than 65 years of age with a history of heart disease, and in older men even without a history of the disease. In both groups, heart attack risk doubled within 90 days of testosterone therapy.

Diagnosis

Endocrine Society[17] suggested assessment of Hypothalamic Pituitary Gonadal axis in diabetes. Diagnosis of androgen deficiency should only be made in men with characteristic symptoms and signs along with unequivocally low testosterone levels.

History suggestive of hypogonadism (such as poor general well being, fatigability, poor motivation, low self confidence, mood and irritability, poor concentration and memory, difficulty sleeping, hot flushes and sweats, loss of hair, loss of height, frequency of shaving) should be taken from each patient. The ADAM Questionnaire is a time tested instrument in this regard.

Testosterone concentrations should be measured preferably in the morning to avoid bias to circadian rhythm. Testosterone concentration peaks around at 8 AM and levels are 20–25% lower around 4 PM in young men.[26] This variation is blunted to some extent in older population; but it still persists. Testosterone concentration is suppressed transiently with illness. Low serum testosterone concentration unequivocally on two different occasions is required to diagnose androgen deficiency biochemically. Wang C *et al.*[27] reported that 30% of men having testosterone concentration less than 300 ng/dL on initial assessment were found to have normal levels on repeat testing.

Total serum testosterone is the initial test because of its easy availablility. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the gold standard for measuring testosterone in plasma.

Free testosterone represents 0.5% to 3% of circulating testosterone. It is measured typically by equilibrium dialysis. Equilibrium dialysis is considered gold standard for free testosterone. Bioavailable testosterone levels are measured by the ammonium sulfate precipitation method. It precipitates SHBG and SHBG-bound testosterone. Unbound and albumin-bound testosterones are left in the supernatant. But, equilibrium dialysis and ammonium sulfate methods are technically challenging and are not widely available in hospital laboratories. Free and bioavailable testosterone concentrations also can be calculated from total testosterone and SHBG concentrations.

After diagnosis of androgen deficiency based on low testosterone level, LH and FSH levels should be measured to determine whether the defect is at the testicular level or the hypothalamic-pituitary level.Primary testicular failure is indicated by elevated LH and FSH and low testosterone. Secondary testicular failure is indicated by low or inappropriately normal LH and FSH and low testosterone level.

The threshold testosterone level below which symptoms and signs occur is not known. Threshold testosterone level below which symptoms and signs will improve following therapy is also not clear. However, 280-300 ng/dl is considered the lower limit of normal range for young healthy men.

The Adam Questionnaire

1. **Do you have a decrease in libido (sex drive)?**
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
7. **Are your erections less strong?**
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Testosterone Preparations

Testosterone is available for therapeutic use in various forms. Testosterone enanthate or cypionate is relatively inexpensive. Usual dose is 100 mg IM weekly or 200 mg IM every 2 weeks. After a single IM injection, serum testosterone levels rise into the supraphysiologic range and then decline gradually into the hypogonadal range by the end of the dosing interval giving rise to peaks and troughs in serum testosterone level. It is the reason behind fluctuation of mood and sexual desire. It can be identified by low serum testosterone levels just before next injection and minimized by reducing dosing interval. Dose usually is titrated by measuring serum testosterone levels at the midpoint of dosing interval.

Transdermal Testosteronemay be used in the form of Testosterone Gel and patch. They are not producing supraphysiologic serum testosterone levels. These are relatively expensive preparations and patients must be motivated for daily applications. Short duration of action makes rapid withdrawal possible.

Testosterone patch is usually applied over scrotal skin which can deliver 2.5 to 5 mg of testosterone daily. Testosterone patch may produce skin irritation. Topical triamcinolone acetonide 0.1% cream can reduce this problem.

Testosterone gel is applied daily in the morning over dry skin of shoulder, arm, abdomen and flanks. But scrotal skin is spared. It may be transferred to others through body contact. But, skin irritation is uncommon with gel form. A steady state of serum testosterone levels is achieved with testosterone gel preparations. 2.5 gm of gel contains 25 mg of

testosterone and 5 gm of gel contains 50 mg of testosterone. 10% of this is absorbed. Starting dose is usually 5 gm of gel daily. After 2 weeks, it is titrated either to 7.5 gm or 2.5 gm based on response.

Testosterone undecanoate formulation in castor oil is administered orally. It is absorbed preferentially through the lymphatics into systemic circulation. First-pass degradation in the liver is spared. It is absorbed better with food. Doses of 40 to 80 mg two or three times daily are typically used. However, the clinical responses are variable and suboptimal. Because of short duration of action, rapid withdrawal is possible.

An injectable preparation of testosterone undecanoate in castor oil has been approved. 1000 mg of testosterone in 4 ml is administered IM in the gluteus muscle followed by another dose 6 weeks later then every 10 to 14 weeks.

Monitoring

Clinical response to testosterone therapy is assessed 3 to 6 months after starting therapy. By this time, most treated persons are expected to have some improvements. Biochemical goal is to achieve serum testosterone in the mid normal range. For testosterone enanthate or cypionate preparation, serum testosterone is measured after 3 to 6 months of therapy mid way between two consecutive injections. For testosterone patch preparation, serum testosterone is measured after 3 to 4 weeks of therapy 8 to 10 hours after application of patch on last night. In case of testosterone gel preparation, serum testosterone is measured after 2 weeks of therapy at any time after application.

Adverse Effects

Testosterone therapy should be avoided in men with metastatic prostate cancer[17] or breast cancer. Because, it has potential to promote growth of these cancers. Testosterone is aromatized to estradiol in peripheral tissues and can exacerbate breast cancer. The candidates also should be checked before Testosterone therapy for preexisting erythrocytosis, severe obstructive sleep apnea, and severe congestive heart failure. Neuromuscular effects of testosterone on the upper airway is responsible for deteriorating obstructive sleep apnea. Post therapy salt and water retention may worsen congestive heart failure. Prostate cancer may manifest as prostate nodule, induration, or elevated PSA. These conditions should lead to a urologic evaluation before testosterone therapy. On the other hand, serum PSA levels are lower in testosterone-deficient men and are restored to normal following testosterone therapy. However, serum PSA levels do not increase progressively in healthy hypogonadal men with replacement doses of testosterone.

The most common testosterone-related adverse events[17] include erythrocytosis, acne, oily skin, and breast tenderness. The frequency of other adverse events like gynecomastia and induction or worsening of obstructive sleep apnea during testosterone therapy is low.

TABLE 1 | Contraindications to testosterone administration[17]

Very high risk of serious adverse outcomes
• Metastatic prostate cancer • Breast cancer
Moderate to high risk of adverse outcomes
• Undiagnosed prostate nodule or induration • Unexplained PSA elevation • Erythrocytosis (hematocrit > 50%) • Severe BPH symptoms as indicated by an American Urological • Association/International Prostate Symptom Score > 19 • Unstable severe CHF (class III or IV)

Table 2 | Potential adverse effects of testosterone replacement[17]

Evidence of association
• Erythrocytosis • Acne and oily skin • Detection of subclinical prostate cancer • Growth of metastatic prostate cancer • Reduced sperm production and fertility
Weak evidence of association
• Gynecomastia • Male-pattern baldness (familial) • Worsening of BPH symptoms • Growth of breast cancer • Induction or worsening of obstructive sleep apnea
Formulation-specific
Oral Tablets • Liver function abnormalities (methyl testosterone) • Lowering of HDL cholesterol (methyl testosterone)
Pellet Implants • Infection and scarring expulsion of pellet
Intramuscular Injections of Testosterone Enanthate or Cypionate • Fluctuation in mood or libido • Pain at injection site • Erythrocytosis (esp. older patients)
Transdermal Patches • Skin reactions at application site
Transdermal Gel • Potential risk for testosterone transference to partner (need to remind patient to cover application sites with a clothing and to wash skin and hands with soap prior to having skin-to-skin contact with another person)
Buccal Tablets • Alterations in taste • Irritation of gums

Testosterone should be discontinued when hematocrit is greater than 54%; therapy may be reinitiated at a lower dose when hematocrit has fallen to a safe level (<50%). Transdermal therapy[28] produces a lesser increase in hemoglobin levels than testosterone esters. Erythrocytosis is possibly through its effects on erythropoietin and stem cell proliferation.[29]

Conclusion

Interactions between insulin resistance and testosterone have been explored over the years revealing a bidirectional

relationship. Different authors are of different opinion regarding use of testosterone in this background. Some have found improvement even in insulin resistance parameters in addition to hypogonadal symptoms. Though this has not been supported by other findings, Emily J. Gianatti *et al.*[30] found that testosterone therapy did not improve glucose metabolism or visceral adiposity in obese men with moderately controlled T2DM. So, we have to wait for an answer revealing safe and working relationship more confidently between these two.

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