32 Male Hypogonadism and Type 2 Diabetes Mellitus

Abstract: In recent years concepts are developing whether male hypogonadism and testosterone deficiency are the factors for developing insulin resistance and subsequent development of T2DM.

This hypothesis developed from the observations that, testosterone deficiency in adult male is associated with T2DM, coronary artery disease and heart failure. Replacement of testosterone hormone to this subset of patients results in improvement of the condition.

Recent studies have shown that male hypogonadism is more prevalent than thought earlier, is strongly associated with metabolic syndrome and may be a risk factor for the development of T2DM and coronary artery disease. Long-term studies are required to establish the relation with these diseases, the effect of testosterone replacement and its long-term safety profile with the exception of increase in haematocrit, which already we know.

The prevalence of both hypogonadism and type 2 DM increases with age. But it is not proved beyond doubt, whether male hypogonadism contributes to the development of T2DM or T2DM leads to the development of hypogonadism or both are the presentations of some age related condition like increased fat mass. This concept, if it is supported by large multicentric studies, a new arena of understanding, treating and preventing diabetes mellitus in men will be opened.

INTRODUCTION

Insulin resistance (IR) is one of the significant features of Type 2 diabetes mellitus (T2DM), and encompasses a spectrum of features like obesity, hyperglycemia hypertension and dyslipidemia mainly. Subsequently gout, non-alcoholic fatty liver diseases, polycystic ovarian syndrome, hyperleptinemia have joined the family of IR. In the last decade concepts are developing whether male hypogonadism and testosterone deficiency can lead to the development of insulin resistance and subsequent T2DM.

This concept developed from the current trials that, testosterone deficiency in adult male is associated with T2DM, coronary artery disease and heart failure. Replacement of testosterone hormone to this subset of patients has shown promises in improvement of the condition.

Definition of Hypogonadism

Hypogonadism in men is classified as:

i. Primary (testicular failure)
ii. Secondary (pituitary/hypothalamic failure)
iii. Mixed

Regardless of age or etiology, men with a total testosterone (8 AM – 10 AM) below 300 ng/dl often develop signs and symptoms, which is detrimental for long term health. But variable opinions regarding lower threshold persist. Endocrine society and American Association of Clinical Endocrinologist (AACE) consider this level as 200 ng/dl, whereas USAFDA accepts the value of 300 ng/dl.[1]

The condition is nomenclatured as androgen deficiency in adult male (ADAM) or more correctly Partial Androgen Deficiency in Adult Male (PADAM) or Endocrine Decline in Adult Male (EDAM). The term andropause is misnomer, because total androgen deficiency does not occur except after surgery, accident and diseases. Though total testosterone estimation is informative in majority, but bioavailable testosterone (albumin bound and free) is more helpful. But they are difficult to perform and costly also. ADAM questionnaire and related signs taken together with the hormone level gives the correct diagnosis.

Hypogonadism and Aging

Several studies have established the proportionate fall of testosterone with age. Total testosterone (TT) in circulation consist of:

i. Sex Hormone Binding Globulin (SHBG) bound testosterone (SHBG-TE) = 58%
ii. Albumin bound testosterone (ABT) = 40%
iii. Free testosterone (FT) = 2%

Age related fall in total testosterone with increase in SHBG level and decrease in bioavailable free testosterone has been observed even if Body Mass Index (BMI) does not exceed 26 kg/m^2 [(2)] Feldmaen, et al[3] observed a decline of total testosterone by 0.8% per year of age, whereas both free and albumin bound testosterone declines at about 2% per year. SHBG levels increased at 1.6% per year. But luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels tend to rise with age.

Tenover, et al[4] observed the fact that the major age related changes in testosterone levels are caused by changes at testicular function and not due to hypothalamic pituitary axis pathway, which is not altered with age. They noted that treatment of aging men with clomiphene citrate, an anti-estrogen agent, could not increase the level of bioavailable testosterone as is seen in younger men even though LH pulse characteristics and bioavailable LH levels were similar in two groups.

Hypogonadism: A Risk Factor for DM and or Metabolic Syndrome

Researches in recent years have provoked the thought whether hypogonadism is a risk factor for development of T2DM or not. Haffner, et al[5] documented that decrease in SHBG in aging female, but not in male can predict development of T2DM. But in 1996, for the first time, multiple risk factor intervention trial (MRFIT) study reported that low level of SHBG and total testosterone may also be predictive for T2DM in men.[6]

Kapoor D, et al[7] in a cross sectional study of 355 Type 2 DM male patients aged above 30 years, showed that low testosterone level is commoner in diabetic men and a significant portion had symptoms of hypogonadism. Overt hypogonadism was seen in 17% of men with low total testosterone and 14% of men with low bioavailable testosterone. Borderline hypogonadism was found in 25% of men with low total and bioavailable testosterone. BMI and WHR negatively correlated with testosterone level with stronger association with WHR. HbA1c > 6.5% was well correlated with lower total testosterone group but not with free or bioavailable testosterone population. Erectile dysfunction was observed in 70% of low testosterone levels and sildenafil non-responders mostly (60%) improved with testosterone therapy.

Corona G, et al[8] assessed the specific contribution of metabolic syndrome and T2DM towards male hypogonadism and the former particularly visceral adiposity was proved to be specifically associated. T2DM cases were associated with hypogonadism in presence of features of metabolic syndrome than its absence.

The Massachusetts Male Aging Study prospectively evaluated 1709 male persons in Boston, during 1987 to 1989 and reevaluated them 7-10 years later.[9] With each decrease of one standard variation in free testosterone (4 ng/dl), an increased risk of 1.58 fold for developing DM was noted. And for each decrease in one standard deviation in SHBG (16 nmol/l) an increased risk of 1.89 fold of DM was also noted. Both values were significant ($p < 0.002$). But questions have been raised about this study because of lack of baseline glucose and insulin levels and the interpretation from self-reporting incidences of diabetes.

In 2002, the investigators of Rancho Barnado Study[10] analyzed 294 men aged 55-89 years. Fasting and 2 hours glucose and insulin levels after 75 G glucose were estimated together with hormone levels. They found that total but not bioavailable testosterone levels were inversely related to subsequent development of DM within 8 years. Low testosterone level had a 2-7 fold higher risk of developing DM after correcting the data for baseline age, BMI, systolic BP. The potential limitation of this study is, each person had only one measurement of testosterone level.

Selvin, et al[11] observed that in sufficiency of free and bioavailable testosterone may be a risk factor for diabetes even when adjusted for age, race, and ethnicity and, more importantly, for adiposity. They hypothesized that androgens may directly influence glucose metabolism and insulin resistance independently of the effects of adiposity. No association with total testosterone was seen in their study.

Low testosterone levels have been observed in association with dyslipidemia and hypertension.[12] Laaksonen, et al have shown hypotestosteronemia is not only associated with the components of metabolic syndrome but also with the metabolic syndrome itself, regardless of BMI.[13] It is a known fact that proinflammatory cytokines like TNFα, IL-6 are associated with metabolic syndrome and testosterone replacement has shown reduction of TNFα, IL-6.[14]

Recent report by Makhsida, et al[15] in 2005, have confirmed that hypogonadism predisposes men to insulin resistance, obesity, abnormal lipids and borderline or overt hypertension. They also concluded that the evidence linking hypogonadism and metabolic syndrome is strong enough to expand the definition of metabolic syndrome and include hypogonadism as a diagnostic parameter in future.

The prevalence of hypogonadism in men is reported to range between 20 to 64%.[16] Corona, et al[17] in an analysis of 1200 men with erectile dysfunction reported hypogonadism in 24.5% among diabetics than 12.6% among non-diabetic men (30.9%). In 2006, HIM study showed greater prevalence of diabetes amongst hypo gonadal men (30.9%) than eugonadal men (17.9%).

Kuopio Ischemic Heart Disease Risk factor Study from Finland in 2003 reported that, non diabetic hypogonadal men, if they were in lowest quartile for testosterone level are 4-fold likely to develop metabolic syndrome, twice as likely to develop DM or metabolic syndrome within an 11 year period. On the contrary, if they had metabolic syndrome at baseline, during 11 year period, chances of developing hypogonadism is 2.9 times more.

New onset hypogonadism is more common (5.7 to 7.4 times) among men with already existing metabolic syndrome and 3 times more common in new onset metabolic syndrome.[18] In an interventional study with 58 obese men with metabolic syndrome prevalence of hypogonadism decreased from 48% at baseline to 9% with very low calorie diet and weight loss of 16.3 kg but increased to 21% with subsequent 2 kg weight gain.[19] Significant improvement in insulin sensitivity, fasting glucose, HDL, Triglyceride were also observed.

Prevalence of Hypogonadism Amongst T2DM

For a longtime, mutual existence of hypogonadism and T2DM has been observed, but any causal relation or inter relation were not established. Barrett Connor, et al[20] between 1972 to 74 evaluated 985 men aged 40 to 79 years. Of them 110 diabetic men had lower testosterone level and lower SHBG level than non-diabetic men. Incidence of testosterone below 350 ng/dl were more in diabetics (21%) than non-diabetic men (13%). Inverse correlation between fasting glucose and testosterone level was a constant failure.

Tan and Pu[21] noted that 64% of diabetics had total testosterone below 300 ng/dl than 38% of non-diabetic persons. All of them had at least one symptom of testosterone deficiency with mean age of 73 years. This study proves low testosterone is more common in older diabetics.

Bioavailable Testosterone and DM

Earlier reports have not estimated the bioavailable testosterone level and whether low testosterone level is due to low SHBG level, cannot be answered. Goodman-Green[22] and Barret-Conner[23] studied 775 male persons about 55 years of age out of which 15% were diabetic. The diabetic group was older than those who had no diabetes and have higher waist/hip ratio (WHR) though mean BMI were same. Both total and bioactive testosterone was inversely correlated with BMI and WHR but only total testosterone was significantly and inversely associated with hyperglycemia. Absence of correlation with bioactive testosterone probably indicates altered level of SHBG production than testosterone production may be the reason behind.

Alteration of SHBG Level

SHBG level usually falls with obesity and increase with aging as with aging muscle mass diminishes and fat mass increases. Commonly occurring factors, which either raise or lower SHBG level, are shown in Table 1.

Higher insulin level due to insulin resistance may suppress hepatic production of SHBG and may exert its link with obesity.[24] But Abate, et al[25] found no difference in SHBG level between diabetic and non-diabetic persons. It is likely that estrogen: androgen ratio regulates the SHBG levels. The combined effect of obesity and aging on SHBG in diabetics is not properly understood. Even in controlled diabetic men (without medicines) higher serum insulin was observed with lower SHBG level compared to age and BMI matched non-diabetic persons.[26] But mean BMI was lower than previous groups studied in USA.

With significant weight loss, SHBG and male hormones usually become normal as observed by Strain, et al.[27] After 12 months of significant weight loss in 19 morbid obese men after vertical gastroplasty, significant decrease in estradiol level and increase in FSH, total testosterone, SHBG were seen which strengthen the idea of adverse effects of obesity on SHBG levels.[28]

Testosterone Secretion in Obese People

Decrease in SHBG and testosterone levels and increase in estrogen level are noted in men with obesity but opposite findings are also reported. Effects of obesity and ageing on different hormones and hypothalamic pituitary testicular (HPT) axis are shown in Table 2.

Two-fold increase in estrone and estradiol levels with normal testosterone level was reported in morbidly obese man by Schneider, et al.[29] In those obese people metabolic clearance rate of testosterone and peripheral conversion of testosterone to estradiol and androstenedione to estrone was increased, together with normal LH and testosterone response to clomiphene citrate, indicating the intactness of HPT axis.

Vermeulen, et al[30] found significant ($p < 0.001$) negative correlation between plasma free testosterone and BMI and a positive correlation between estradiol and BMI in a population of 35 obese men (BMI > 30 kg/m^2). LH pulsatility was similar in obese and non-obese group but mean diurnal LH pulse amplitude was lower in obese. This reflects the defect to be at the level of hypothalamic pituitary axis.

The observation that dexamethasone suppresses estradiol, estrone, androstenedione, SHBG but not LH and testosterone, suggest the fact that elevated estrogen level in obese are dependent upon adrenal hormones.[31] Endogenous opioids may suppress gonadotrophic releasing hormones in obese men.[32] Lima, et al[33] after applying weight reduction with 1200 cal diet and dexfenfluramine 15 mg twice daily in obese man, concluded that free testosterone increases with weight reduction and dependent upon the degree of obesity.

Attempts have been made to study the effect of insulin and glucose level on testosterone levels separately. Pasquili, et al[34] by suppressing insulin level by diazoxide for 7 days observed the reduction of testosterone (total and free) but increased levels of SHBG, LH in both obese and nonobese men. In subsequent studies[35] they performed acute hyperinsulinemic – euglycemic clamp study in normal and obese man. In obese group basal testosterone was lower but significantly increased during clamp study suggesting the possibility that insulin might effect testosterone secretion. In young men hypoglycemic hyperinsulinemic clamp study was performed and suppression of testosterone was seen with hypoglycemic but not with hyperinsulinemia.[36] Infact in young adult Type 1 DM with insulin deficiency testosterone levels are raised.[37]

All the observations taken together suggest that, low SHBG levels are negatively related to obesity and serum insulin levels. Free testosterone may be normal in men with moderate obesity but fall with increasing obesity.

Testosterone Concentrations in Type 1 and Type 2 DM

Tomar R, et al[38] compared 50 age matched T1DM and 50 T2DM patients and observed normal total testosterone with consistently high normal or elevated SHBG level in T1DM cases together with normal free testosterone, LH and FSH.

But in T2DM cases low total (48%) and free (26%) testosterone concentration with inappropriately low LH and FSH levels were seen. Prevalence of low total and free testosterone was seen in 0 and 6% cases of T1DM. Thus, hypogonadotrophic hypogonadism in T2DM is specific for the disease and not the effect of diabetes or hyperglycemia per se. Lower prolactin level in T2DM than T1DM, which indicates defect in HP axis at dopaminergic level, was also noted. Total daily insulin dose and not BMI was a significant indicator of SHBG levels in T1DM, HbA1c did not correlate to any of the parameters of both Type 1 and Type 2 DM. This study suggests that higher levels of BMI, even in Type 1 DM may develop hypogonadism.

Testosterone Replacement

If biochemical testosterone deficiency is associated with signs and symptoms, necessity of replacement should be considered. Testosterone therapy increases muscle mass in all age groups but reduction in fat mass is seen in middle aged and older men.[39] Marin, et al[40] studied the effect of testosterone or dihydrotestosterone gel for 9 months in testosterone deficient (< 4.5 ng/ml) 31 obese men. Significant reduction in visual fat and improvement in glucose disposal were noted with testosterone but not with dihydrotestosterone, which produced improvement is higher doses only.

The improvement in insulin sensitivity may be due to changes in body composition and by inhibition of lipoprotein lipase activity leading to accelerated release and decreased uptake of triglycerides in abdominal adipose tissues. Reduction is adipocytes results in lower free fatty acids, which improves insulin sensitivity and beta cell function. Increase in deposition of triglycerides in adipocytes increases aromatase conversion. This converts testosterone to estradiol, which inhibits lipoprotein lipase and in turn leads to more fat deposition, lower testosterone level and greater degree of hypogonadism. Leptin level which increase in obesity causes further lowering of androgen level.[41]

Simon, et al reported significant improvement in insulin sensitivity after 3 months of dihydrotestosterone gel.[42] Further evidence of association of hypogonadism and insulin biokinetics is documented in the treatment of prostatic carcinoma. Treatment with gonadotrophin releasing hormone (GnRH) agonists has been shown to develop increase in insulin level.[43] Surgical castration in prostatic carcinoma has shown improvement in insulin and glucose level.[44]

Testosterone treatment has been shown to reduce insulin resistance in obese men and to decrease total cholesterol in hypogonadal men with coronary artery disease, even in those taking statins. Study in 2 diabetic men showed improvement in glycemic control but conflicting reports is there also.[45]

Boyanov, et al have reported a significant reduction in fasting blood glucose and HbA1c after 3 months of testosterone replacement in poorly controlled diabetics.[46]

Kapoor D, et al[45] studied 24 hypogonadal men of T2DM with testosterone replacement and observed improved fasting insulin sensitivity (HOMA index – 1.73 ± 0.67, $p = 0.02$) reduction of HbA1c ($-0.37 \pm 0.17\%$, $p = 0.03$), of fasting plasma glucose (-1.58 ± 0.68 mmol/l, $p = 0.03$), of waist hip ratio (-0.4 ± 0.17 mmol/l, $p = 0.03$) but no change with other lipid parameters and blood pressure also.

Jockenhovel, et al[47] have demonstrated improvement in leptin level from baseline higher level in ageing men with hypotestosteronemia.

Emerging evidence suggest improvement in several or some parameters of metabolic syndrome with replacement therapy. But long-term studies of larger cohort are necessary. Kapoor D, et al[48] observed that testosterone replacement decreases leptin and adiponectin but not inflammatory markers up to 3 months but pro-inflammatory markers were high at baseline level with low testosterone T2DM patient.

Licinio J, et al[49] also have shown that leptin replacement in leptin deficient adults with morbid obesity results in profound weight loss, resolution of T2DM and hypogonadism.

Hypogonadism and Cardiovascular Health

No clear link between testosterone level and cardiovascular mortality/morbidity has been established till date. No long-term studies with testosterone replacement in stroke, deep vein thrombosis and myocardial infarction has been published. But testosterone has shown to be positively associated with HDL cholesterol and negatively with hypertension, hyperlipidemia and prothrombotic factors. Majority of studies in a systemic review of 35 cross- sectional studies reported that low testosterone is associated with higher prevalence of coronary artery disease.[50]

Crossover study in men with ischemic heart disease and hypogonadism reported that the time to 1 mm of ST depression increased, total cholesterol decreased, exercise time is increased and mood improved with testosterone.[51] Testosterone therapy also improves Intima-media thickness and arterial plaque score.[52] Jones RD, et al[53] showed improvement in myocardial ischemia and Kang SM[54] demonstrated improvement in endothelial function by brachial artery vasoreactivity.

Pugh PJ, et al in 2003[55] have established the role of testosterone in improving NYHA class and decreased peripheral vascular resistance in chronic heart failure.

Philips, et al[56] noticed that hypotestoronemia might be a risk factor for coronary atherosclerosis in men. The Massachusetts male ageing study[9] supports the hypothesis that dehydroepiandrostenedione another androgen like testosterone when becomes deficient can predict ischemic heart disease.

Bhatia V, et al[57] in a study of 70 Type 2 DM patients observed mild normocytic normochromic anemia with normal or high erythropoietin and raised C-reactive protein (CRP). Because inflammatory mediators interfere with insulin signal transduction, they may result in hypogonadotrophic hypogonadism. Because of high CRP level, hypotestoronemia in anemic diabetics can produce increased risk of atherogenesis.

Secondary Hypogonadism and Diabetes Mellitus

This condition is observed with Prader-Willi syndrome (PWS), Klinefelter syndrome and Hemochromatosis. DM is not the diagnostic criteria for PWS but found in 20% of cases. DM is probably due to obesity leading to insulin resistance because of decrease in oxytocin neuron and leptin resistance. Hypogonadism is mostly hypothalamic is origin.

Miscellaneous Abnormality is Hypogonadal T2DM

Higher incidence of obstructive sleep apnea is also reported in hypogonadism with T2DM patients, which improves with CPAP treatment but worsened by testosterone therapy.[58] In a subset of hypogonadal diabetic men low bone minimal density and higher chances of fracture was noted in selected bones like arms, ribs than legs, hip and spine.[59]

CONCLUSION

Multiple studies have shown that testosterone deficiency in men is associated with Type 2 diabetes and metabolic syndrome, coronary artery disease and heart failure. Testosterone replacement has also shown to improve the above conditions. But in absence of large long duration multicentric studies, we cannot allow hypogonadism to join as a family member of metabolic syndrome at present, and cannot also allow routine recommendation of testosterone replacement to treat or prevent metabolic syndrome or diabetes mellitus. But physicians should be mindful to screen for metabolic syndrome and diabetes mellitus in all cases of hypogonadism and vice versa. As an isolated case, they can try testosterone replacement after discussing with the patient regarding advantages and disadvantages more so, in cases of sexual dysfunction and develop a novel approach. But watch for complications like erythrocytosis and prostatic carcinoma should always guide these approaches. This new concept also indulges us to think whether female sex hormone has got any equivalent role in women or not.

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1. **American Association of Clinical Endocrinologists (AACE) criteria to diagnose hypogonadism consider testosterone level to be:**
   A. Below 200 ng/dl
   B. 200-300 ng/dl
   C. 300-375 ng/dl
2. **Low testosterone levels have been observed in association with:**
   A. Dyslipidemia
   B. Hypertension
   C. Hyperuricemia
3. **Testosterone treatment in obese hypogonadal men has been shown to reduce:**
   A. Insulin resistance
   B. Decrease total cholesterol
   C. Decrease HDL
4. **With significant weight loss:**
   A. SHBG and male hormones become normal
   B. Decrease in estradiol
   C. Increase in FSH, total testosterone
   D. All of the above
5. **Incidence of obstructive sleep apnea in hypogonadism with T2DM:**
   A. Increased
   B. Decreased
   C. No change

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1. A 2. A, B 3. A, B 4. D 5. A Multiple Choice Questions