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Research Article

Association between androgen deficiency and metabolic syndrome in men with type 2 diabetes mellitus

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Abstract

Objectives: This study aimed to- 1) assess the association of AD with the metabolic syndrome (MetS) in Saudi men with T2DM, 2) determine which component of the MetS that mostly associated with AD in these patients

Methods: In this retrospective study sixty six Saudi men with T2DM were participated. Venous blood samples were collected in plain vacutainers from all the subjects. Serum glucose and lipid profile were measured using standard laboratory procedures. Serum total testosterone (TT) and sex hormone binding globulin (SHBG) were measured by ELISA. AD was defined according to Endocrine Society recommendation, while MetS was defined based on International Diabetes Federation criteria.

Results: Patients showed marked dyslipidemia and significantly low TT and SHBG; 27.3% of patients have AD among which 43.5 % have MetS. Multivariate analysis revealed that obesity (OR 4.553, 95% CI: 1.093 - 18.957; P = 0.037) was the most component of the MetS that associated with AD. Total testosterone was negatively correlated to BMI (r=- 0.480, p=0.000), TG (r=- 0.397, p=0.004); but positively to SHBG (r= 0.706, p <.001).

Conclusion: Obesity as a core component of MetS is significantly associated with hypogonadism in T2DM. With the ongoing obesity epidemic, we believe that the control of body weight and encouragement of physical activity may impact on the reduction the consequences of AD among obese type 2 diabetics

Keywords: type 2 diabetes, metabolic syndrome, androgen deficiency, testosterone, Saudi Arabia.

1. Introduction

Projections of the worldwide prevalence of type 2 diabetes for the near future provide an alarming picture because of population growth, ageing and increased prevalence of obesity and physical inactivity.[1, 2] Obesity, in Saudi Arabia, is a growing problem with an overall prevalence of 35.5% which is associated with major health problems such as diabetes mellitus, coronary artery disease and stroke.[3]

Androgen (testosterone) deficiency (AD) has recently come to the forefront of the medical literature after being ignored for decades.[4] Hypogonadism is a clinical condition comprising both symptoms and biochemical evidence of testosterone deficiency.[5] AD is characterized by symptoms, including loss of muscle mass and strength, increased visceral fat mass, reduced libido, erectile dysfunction, loss of sexual hair, increased osteoporosis, lethargy, lack of energy, and changes in mood.[6] The burden of AD in men with diabetes has become increasingly apparent in population-based studies. Cross-sectional studies have found that between 20 and 64% of men with diabetes have hypogonadism.[7] Moreover, there is evidence that testosterone replacement can reduce insulin resistance in men with type 2 diabetes.[8] In addition, testosterone therapy has been demonstrated to reduce total body fat and visceral adiposity in older men with low/low-normal baseline testosterone levels.[9, 10] Hence, the Endocrine Society of clinical practice recommends screening type 2 diabetic men for testosterone deficiency due to the high prevalence of hypogonadism in these patients and the non-specific signs and symptoms of AD.[11 - 13]

Recently, the close association between hypogonadism and metabolic syndrome has received more attention.[14] Few studies conducted on Saudi population have reported that nearly one-third of Saudi patients with the component of hypogonadism were diabetics.[15] Moreover, in a randomized cross sectional study; the prevalence of metabolic syndrome among Saudis men with type 2 diabetes was 19.49% with dyslipidemia and obesity were the commonest components among patients.[16] We aimed in this retrospective cross-sectional study to 1. Assess the association of androgen deficiency with the metabolic syndrome (MetS) in Saudi men with type 2 diabetes mellitus, 2. Determine which component of the MetS that mostly associated with androgen deficiency in these patients.

2. Materials & Methods

2.1 Study design & population

This retrospective study was conducted in the Biochemistry laboratory, Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, Saudi Arabia fromOctober2012 to April 2013.

Sixty-six Saudi men with type 2 diabetes mellitus (range of age 40 – 73 years) were recruited and participated from Diabetes center, King Fahd Specialist Hospital- Buraidah. Diabetes was diagnosed as a fasting blood glucose ≥126 mg/dL according to the American Diabetes Association criteria.[17] The inclusion criteria for recruitment of type 2 diabetics for participation in the study were: Saudi citizen, male, age 40 years old or more.

Another forty age-matched healthy men without any chronic illness (such as coronary artery disease, hypertension, diabetes and hyperlipidemia) and medication were recruited from the community as a control group for evaluation of serum total testosterone (TT) and sex-hormone binding globulin (SHBG).

2.2 Sample collection & serum preparation

Blood samples from patients and controls were drawn in the morning in one plain vacutainer (4 ml) for each participant. Serum was obtained after centrifugation at 3000 r.p.m for 15 minutes and frozen in aliquots at -80^0 C until analysis.

2.3 Measurements of Body Mass Index (BMI)

Body weight (in light clothing without shoes) and height were measured for each patient. BMI was used to estimate the degree of obesity, and was calculated as weight (kilograms) divided by height (metres) squared. Patients were categorized as normal if BMI < 25 kg/m^2, overweight if BMI between 25-29.9 kg/m^2, and obese if BMI ≥ 30 kg/m^2 based on WHO criteria.[18]

2.4 Measurement of blood glucose & lipid profile

Sera levels of glucose, cholesterol, triglyceride "TG", and HDL-cholesterol "HDL-C" were measured by the Hospitex Eos Bravo clinical chemistry analyzer using commercial kits purchased from Human Diagnostics (Wiesbaden, Germany). LDL-cholesterol "LDL-C" was calculated by using the Friedewald equation: LDL = total cholesterol – HDL – (triglycerides/5).

2.5 Estimation of serum levels Total testosterone & SHBG

Sera levels of total testosterone and SHBG were measured by competitive immunoassay methods (WUHAN EIAAB SCIENCE. CO. LTD, CHINA) using the bioMerieux Reader 250 version 2.0.5. The detection range of the assays were 0.15- 10.0 ng/ml for total testosterone and 7.80 – 500 nmol/l for SHBG.

Briefly, the microtiter plates provided from manufacturer had been pre-coated with an antibody specific to testosterone or SHBG. During the reaction, testosterone or SHBG in the sample or standard competes with a fixed amount of biotin-labeled testosterone or SHBG. Excess conjugate and unbound sample or standard were washed from the plate. Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. Then a TMB (3,3′,5,5′-tetramethylbenzidine) substrate solution was added to each well. The enzyme-substrate reaction was terminated by the addition of a sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentrations of testosterone or SHBG in the samples were determined by comparing the optical density of the samples to the standard curve

At cut-off level of TT equal to 10.4 nmol/l, the patients were classified into hypogonadal group (TT < 10.4 nmol/l) OR eugonadal group (TT≥10.4 nmol/l).[19]

2.6 Definition of Metabolic Syndrome (MetS)

In this study we adopted the new International Diabetes Federation (IDF) definition.[20] for MetS with a little bit modification. Since all patients in this study were previously diagnosed diabetes, we arbitrary considered more than 150 mg/dl blood glucose as a cutoff for the target group.

The patients were considered to have the MetS if they have BMI > 30Kg/m^{2}plus any two of the following: TG ≥ 150mg/dL, HDL-C: <40 mg/dL, using anti-hypertensive drugs, and blood glucose ≥150mg/dL.

2.7 Ethical consideration

According to the Helsinki declaration guidelines, this study was approved by Institutional Review Committee of the authors' institute. Verbal consent was obtained from each subject after thoroughly explanation the goals of the study. Participation was voluntary and confidentiality of all participants was maintained as no names were requested.

2.8 Statistical analysis

The data collected and analyzed using the statistical package for social sciences (SPSS) software (version 17). Descriptive statistics (mean ± standard deviation or number (percentage) were used for demographic and clinical variables. Comparison of variables between hypogonadism & eugonadism in type 2 diabetics were performed with an unpaired t-test and chi-square test for continuous and categorical variables, respectively. The Pearson correlation was used to examine the relationship between TT level and BMI, TG, HDL, SHBG. Univariate and multivariate analyses were performed; with hypogonadism as the dependent variable, and components of metabolic syndrome as independent variables. Significance considered when a *P*- value was less than 0.05.

3. Results

3.1 Baseline characteristics and prevalence of androgen deficiency among Saudi patients with type 2 diabetes

Mean age of diabetics was 59.58 ± 8.1 years (median61.50; 95% CI 57.58 -61.58 years) with mean BMI almost equal to 30 Kg/m^2, which reflects that most of the patients were obese or overweigh (median 28.7; 95% CI 27.41 – 30.61 kg/m^2).Lipid profile findings documented that type 2 diabetics have dyslipidemia according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines.[21]

Based on the guidelines of the European Endocrine Society; serum TT was below 10.4 nmol/l in 27.3% Saudi patients with type 2 diabetes. The median (min-max) serum level of TT was 7.52 (5.98 – 10.10) nmol/l and 11.89 (10.41 – 15.50) nmol/l for hypogonadal and eugonadal type 2 diabetics respectively figure 1.

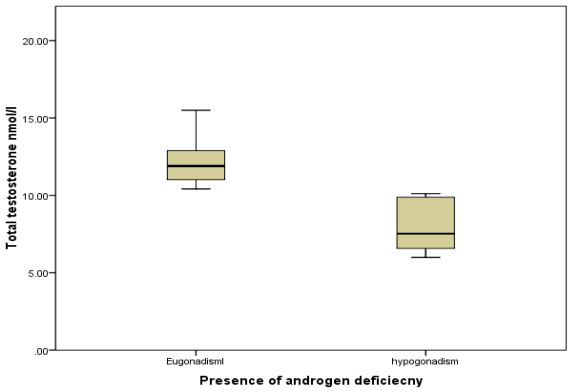

Figure 1: Boxplot chart of serum total testosterone levels (nmol/l) in Saudi type 2 diabetic patients Eugonadal group and Hypogonadal group. The median (min-max) serum level of total testosterone was 7.52 (5.98 – 10.10) nmol/l and 11.89 (10.41 – 15.50) nmol/l for hypogonadal and eugonadal type 2 diabetics respectively

Moreover, except for the BMI, SHBG, TT levels, no significant difference was recorded between hypogonadal group and Eugonadal group in type 2 diabetics for all investigated parameters.

Demographic and clinical characteristics of hypogonadal & Eugonadal type 2 diabetics are listed in table 1

Table 1: Demographic and clinical characteristics of hypogonadal & Eugonadal type 2 diabetics: data represented as mean ± standard deviation. Classification based on the European Endocrine Society recommendation at cutoff 10.4 nmol/l of normal total testosterone.

Variable	All patients	Eugonadism TT≥10.4 nmol/l	Hypogonadism TT<10.4 nmol/l	*P*-value
Number (%)	66 (100%)	48 (72.7%)	18 (27.3%)	
Age (years)	59.58 ± 8.1	59.96±8.7	58.56±6.9	0.537
Weight (kg)	81.00±24.7	78.33±24.2	88.11±25.2	0.153
BMI (kg/m^2)	29.01±6.5	27.61±4.9	33.00±8.5	0.003*
BSL(mg/dl)	191.11±6.2	188.25±7.7	197.53±10.6	0.496
Diabetes Duration (yrs)	12.91±4.7	12.73±4.8	13.39±4.4	0.614
TG (mg/dl)	157.46±6.3	148.69±7.3	173.56±11.0	0.058
TC(mg/dl)	214.39±5.4	216.06±6.4	210.79±10.3	0.654
[l]HDL -C(mg/dl)	39.90±0.6	40.00±0.5	39.70±1.5	0.810
LDL-C (mg/dl)	145.58±5.1	146.35±5.9	144.03±10.3	0.835
TT (nmol/l)	10.91±0.3**	12.00±1.1	8.01±1.5	<0.001*
SHBG(nmol/l)	27.64±1.1***	31.55±0.7	17.20±1.1	<0.001*

Abbreviations: BMI, body mass index; BSL, blood sugar level; TG, Triglyceride; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; TT, total testosterone; SHBG, sex hormone binding globulin
* *P*-value <0.05; a: p value compared diabetics in hypogonadal group to eugonadal group
** TT level in diabetics was significantly lower when compared to age- matched healthy men (14.11±0.6 nmol/l; p<0.001)
*** SHBG in diabetics was significantly lower when compared to age- matched healthy men (46.33±1.9 nmol/l, p<0.001)

3.2 Prevalence of MetS and its components among hypogonadal Type 2 diabetes group

Among the patients in hypogonadal group, 43.5 % of diabetics fulfilled the criteria for MetS. When we further investigated the relationship between the components of MetS and hypogonadism, and found that central obesity and elevated TG were the significant key elements of MetS that associated with hypogonadism in Saudi men with type 2 diabetes shown in table 2.

Table 2: Prevalence of metabolic syndrome and its components among hypogonodal/ Eugonodal type 2 diabetics: data represented as number (%)

Variable	Eugonodal group	Hypogonodal group	*P*-value
MetS (+)	13 (56.5%)	10 (43.5%)	0.031*
MetS (-)	35 (81.4%)	08 (18.6%)	
Central Obesity (BMI > 30 Kg/m^2)	12 (25.0%)	11 (66.7%)	0.004*
Elevated TG (TG > 150 mg/dl)	13 (27.1%)	13 (72.2%)	0.001*
Decreased HDL-C (HDL-C < 40 mg/dl)	13 (56.5%)	10 (43.5%)	0.069
Raised Blood Pressure (using anti-hypertensive Medication)	28 (58.3%)	13 (72.2%)	0.300
[ll]BSL >150 mg/dl	29 (60.4%)	13 (72.2%)	0.262

Abbreviations: MetS, Metabolic syndrome, BMI, body mass index; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; [l]BSL, blood sugar level

These findings were confirmed by logistic regression analysis (table 3); univariate analysis showed that central obesity (BMI > 30 Kg/m$^{2)}$ and elevated TG (> 150 mg/dl) were the most components of MetS that associated with Hypogonadism (OR 5.500, 95% CI: 1.673 - 18.080; P = 0.005 and OR 4.000, 95% CI: 1.151 - 13.899; P = 029 respectively). However, when analyzing all components of MetS together, the multivariate analysis revealed that only central obesity was associated with hypogonadism in type 2 diabetics (OR 4.553, 95% CI: 1.093 - 18.957; P = 0.037).

Table 3: Association between Hypogonadism and components of metabolic syndrome in type 2 diabetics using logistic regression analysis

components of MetS	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
BMI > 30 Kg/m^2	5.500	1.673 - 18.080	0.005*	4.553	1.093 - 18.957	0.037*
TG > 150 mg/dl	4.000	1.151 - 13.899	0.029*	3.251	0.678 - 15.601	0.141
HDL-C < 40 mg/dl	2.564	0.750- 8.769	0.133	0.867	0.159 - 4.721	0.869
Raised Blood Pressure: Yes	1.857	0.571– 6.046	0.304	1.885	0.345 - 10.304	0.464
BSL >150 mg/dl	0.897	0.229 - 3.517	0.876	1.122	0.173 - 7.255	0.904

BMI: body mass index; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol; BSL: blood sugar level
*P**< 0.05

3.3 Correlation between total testosterone and components of metabolic Syndrome

We performed Pearson correlation analysis between serum concentrations of TT and BMI, TG, HDL-C, SHBG. Our findings showed that TT was negatively correlated to BMI (r=- 0.480, p=0.000), TG (r=- 0.397, p=0.004); but positively correlated to SHBG (r= 0.706, p <.001); Fig 2 a,b,c,d

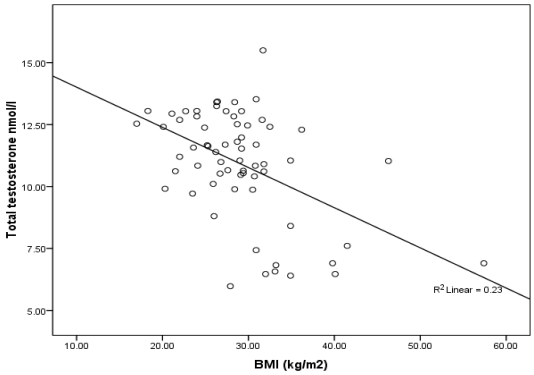

Fig 2.a. Relationship between level of serum total testosterone (nmol/l) and BMI (Kg/m^2) in type 2 diabetics r = -0.480*, p =0.000; * correlation is significant at the 0.01 level (2-tailed)

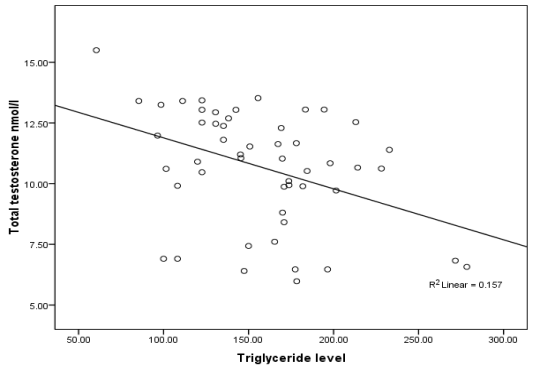

Fig 2.b. Relationship between level of serum total testosterone (nmol/l) and TG (mg/dl) in type 2 diabetics r = -0.397*, p =0.004; * correlation is significant at the 0.01 level (2-tailed)

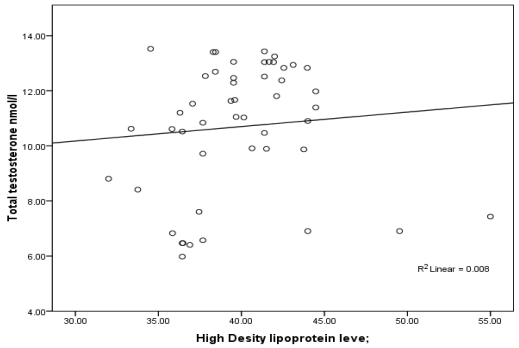

Fig 2.c. Relationship between level of serum total testosterone (nmol/l) and HDL (mg/dl) in type 2 diabetics r =0.091, p =0.536

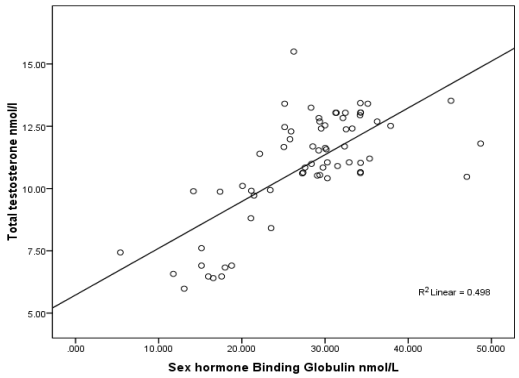

Fig 2.d. Relationship between level of serum total testosterone (nmol/l) and sex hormone binding globulin (nmol/l) in type 2 diabetics r = 0.706*, p <.001*correlation is significant at the 0.01 level (2-tailed)

4. Discussion

Lifestyles have changed in developed countries as physical activity has become less frequent and, simultaneously, the supply of food has substantially overtaken demand. These changes have resulted in an increasing prevalence of overweight and obesity among the populations of these countries, especially during the past two decades. As a consequence, a complex pathophysiological disorder consisting of an accumulation of visceral adipose tissue, dyslipidemia, insulin resistance and hypertension has emerged: the metabolic syndrome.[22]

Consistent with reports from previous studies,[23-26] data from this study confirms the significantly low levels of serum total testosterone in Saudi patients with type 2 diabetes when compared to healthy controls. Moreover, more than one quarter of diabetic patients showed hypogonadism at cut-off 10.4 nmol/l of total testosterone based on the European Endocrine Society.

Testosterone not only mediates male reproductive/sexual functions but also has a profound impact on the health of bones and muscles, on metabolic parameters related to the development of diabetes mellitus and cardiovascular disease. Testosterone deficiency profoundly impairs male health resulting in increased morbidity and decreased quality of life.[27]

The physiopathology of low testosterone levels in type 2 diabetics is not well defined. It might be a result of insulin resistance (the characteristic feature of type 2 diabetes) which may result in part an alteration in Leydig cell function. In a large cohort, it has been reported a positive correlation between serum total testosterone levels and insulin sensitivity, independent of sex hormone-binding globulin (SHBG).[28] Another explanation of the low testosterone levels may be as a consequence of low levels of SHBG encountered in obese men.[29] The latter explanation supported by our findings of the low levels of serum SHBG and clear obesity in diabetic patients in this study. Interestingly, serum total testosterone in Pearson correlation was associated positively with SHBG, but inversely with BMI (Fig 2 a & d). Recently, Vikan *et al* reported that, in a population-based prospective study, men with low testosterone and low SHBG levels had an increased risk to develop type 2 diabetes mellitus which appeared to be dependent on obesity.[30]

Obesity, which is a core element of metabolic syndrome,[14] has been associated with an increased incidence of male factor infertility.[31] Concurrently, emerging evidence reported that the level of plasma testosterone is related to features of the metabolic syndrome.[32] In a prospective cohort study by Laaksonen *et al*,[33] patients with the metabolic syndrome at baseline have increased odds of developing hypogonadism, and patients with low testosterone levels were more likely to develop the metabolic syndrome during an 11-year follow up period. Our data documented that 43.5% of type 2 diabetics with hypogonadism fulfilled the criteria of metabolic syndrome based on the new IDF definition. Furthermore, multivariate logistic regression analysis for the components of metabolic syndrome revealed that central obesity was strongly associated with the development of hypogonadism in type 2 diabetics. Diabetics who have BMI more than 30 kg/m^2 were approximately five times more at risk to develop hypogonadism compared to patients with BMI equal to or less than 30 kg/m^2.

The increase in adipose tissue mass in obesity may result in increased aromatase activity, which metabolizes testosterone to oestradiol. An increase in estradiol concentrations in turn may potentially suppress the hypothalamic secretion of gonadotropin- releasing hormone and pituitary gonadotropin secretion. This would result in the reduction of both testosterone secretion by Leydig cells and spermatogenesis in the seminiferous tubules.[34] A recent study reported that total and free estradiol concentrations in type 2 diabetic men with hypogonadotropic hypogonadism were significantly lower than in those without hypogonadotropic hypogonadism.[35] Moreover, Testosterone is known to inhibit the enzyme lipoprotein lipase, which is the major regulator of triglyceride uptake into adipocytes. A fall in testosterone levels leads to greater activity of lipoprotein lipase, causing increased triglyceride storage and proliferation of adipocytes, with this in turn exacerbating insulin resistance. The greater amount of adipocytes then drives the cycle leading to a further reduction in the circulating testosterone level.[36] This explanation is supported by our finding of the inverse relationship between total testosterone levels and triglyceride level as shown in figure 2-b.

5. Conclusion

In summary, the findings of this study clearly show that both testosterone and its binding protein (SHBG) have low levels in type 2 diabetics. Among the metabolic syndrome components, central obesity was significantly associated with androgen deficiency in type 2 diabetics. With the ongoing obesity epidemic, testosterone deficiency is necessary to be checked especially in type 2 diabetics. Moreover, lifestyle intervention to encourage weight loss and physical activity may increase testosterone and hence decrease consequences of androgen deficiency among type 2 diabetics and the risks expected from testosterone replacement therapy as well.

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