Relationship between serum testosterone and sex hormone- binding globulin levels and some metabolic changes in Iraqi men with type 2 diabetes mellitus

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العلاقة بين مستوى التستيرون الكلي والكلوبيولين المرتبط بالهورمونات الجنسية في مصل الدم وبعض التغيرات الايضية لدى الرجال العراقيين المصابين بالسكري من النوع 2

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الخلاصة

تهدف هذه الدراسة الى تقييم العلاقة بين هرمون التستوستيرون الكلي في مصل الدم (S.Testosterone) والكلوبيولين المرتبط بالهرمونات الجنسية (SHBG)،والمظاهرالرئيسية للمتلازمة الايضية لدى الرجال مصابين بالسكري من النوع 2.

في هذه الدراسة تم اخذ مائة وستون مريضا يعانون من السكري النوع 2 (T2DM). تم تسجيل الخصائص الاتية : العمر والجنس ومدة T2DM ومؤشر كتلة الجسم (BMI) وضغط الدم . تم قياس الهرمونات الاتية في مصل الدم (التستوستيرون الكلي والكلوبيولين المرتبط بالهرمونات الجنسية وهرمون البولاكتين). تم قباس شحوم مصل الدم وشملت (الكوليستيرول الكلي TC و الكلسيريدات الثلاثية (TG) والكوليستيرول مرتفع الكثافة (HDL-C) . كان متوسط اعمارالمرضى 5.7± 49.8 سنة، ومتوسط مدة المرض كان 5.2± 5.4 سنة وأن مؤشر كتلة الجسم (BMI) لمجموعة الدراسة كان ضمن تصنيف زائدي الوزن أو السمنة. كانت جميع مكونات الدهون ضمن المعدل الطبيعي بينما كانت مستويات الكلوبيولين المرتبط بالهرمونات الجنسية والتستوستيرون الكلي ضمن المعدل الطبيعي ولكنها من القيم المنخفضة(4.49 ±2.11 و 28.88±18.12 على التوالي) في حين كان مستوى البرولاكتين في الدم ضمن المعدل الطبيعي ولكنه من القيم العالية (9.42±11.22) . عندما تمت مقارنة القياسات وفقا لدراسة وجود واحد أو أكثر من المظاهر اللرئيسية للمتلازمة الأيضية فقد كان هناك انخفاضا معنويا في قيمة متوسط مستوى هرمون التستوستيرون لدى مرضى السكري الذين يعانون من السمنة مقارنة بالذين لا يعانون من السمنة (3.89 ± 1.87 مقابل 4.79 ± 2.17 ng/ ml، P<0.001). عند وجود ارتفاع في ضغط الدم بالاضافة الى السمنة والسكري فقد انخفض بشكل معنوي مستوى SHBG مقارنة مع مرضى السكري الذين لديهم ارتفاع ضغط الدم ولا يعانون من السمنة (25.16 ± 13.42 مقابل 33.58 ± 13.73 ng/ mlعلى التوالي، P <0.05). إذاكان هناك ارتفاع في ضغط الدم بالاضافة الى وجود البدانة وكذلك انخفاض HDL-C فقد كان هناك انخفاض معنوي في SHBG والتستوستيرون على حد سواء (30.63 ± 14.93 مقابل 40.7 ± 6.33 ng/ mlو 3.73 ± 1.9 مقابل 5.57 ± 1.53 ng/ mlعلى التوالـي، p <0.01).

في الخاتمة **فأن** مرضى السكري من النوع 2 (T2DM) في هذه الدراسة قد أظهروا سيطرة سيئة على نسبة السكر في الدم كما وجد ان هناك انخفاض معنوي في مستوى هرمون التستوسترون عند هؤلاء الذين يعانون من السمنة. إن تراكم مظاهر أساسية أخرى للمتلازمة الايضية وهي أرتفاع ضغط الدم وانخفاض (HDL-C) يؤدي الى انخفاض معنوي في مستوى التستوستيرون والكلوبيولين المرتبط بالهرمونات الجنسية على حد سواء. أن السمنة، من بين المظاهر الأساسية الأخرى للمتلازمة الايضة ، يبدو أن لها الأثر الرئيسي الكابح لهرمون التستوستيرون والكلوبيولين المرتبط بالهرمونات الجنسية عند مرضى السكري من النوع 2

Abstract

The present study aimed to assess the interrelationship between serum total testosterone (S.Tes) as well as sex hormone binding globulin (SHBG) and the main components of metabolic syndrome (MetS) in type 2 diabetic men.

One hundred and sixty patients having T2DM were enrolled in this study. The following characteristics were reported: age, gender, duration of T2DM , Body mass index (BMI) and arterial blood pressure.. Serum hormonal profile analyses (S.Tes, SHBG and prolactin). Serum lipid analyses (T.ch TG, HDL-C, and LDL-C).

The mean age of study subjects was 49.8 ±5.7 years and the mean duration of disease was 5.4±5.2 years. Body mass index (BMI) of study group was found to be within the range of either overweight or obese class . The means of HbA1c ratio and FSG levels were 9.4 % ± 2.1 and 200.9 ± 75.2 mg/dl respectively which indicated that our patients were in a bad glycemic control. All components of S. lipid profile were within normal range . Serum Testosterone and SHBG levels were within normal range but in the low values(4.49±2.11 ,28.88±18.12 ng/ml respectively) while serum prolactin level was within normal range but in the high values(11.22±9.42 ng/ml). When study analytes were compared according to the presence of one or more metabolic syndrome characteristic then there was a significant decrease in mean value of testosterone level between obese and non obese diabetics (3.89±1.87 vs. 4.79±2.17 ng/ ml, $P < 0.001$) . If hypertension was present in addition to obesity and diabetes then SHBG level was also significantly decreased in comparison with diabetics who were hypertensive but not obese (25.16±13.42 vs. 33.58±13.73 ng/ ml respectively , $P < 0.05$). If hypertension and obesity were present as well as lower HDL-C then significant decreases in both S. SHBG and S. Tes were detected ((30.63±14.93 vs. 40.7± 6.33 ng/ ml and 3.73±1.9 vs. 5.57±1.53 ng/ ml respectively , $P<0.01$).

In conclusion; our T2DM patients have a bad glycemic state and are characterized by a significantly lower S. Tes mean level if they were obese. Still, the accumulation of other main characteristics of MetS which included hypertension and lower S. HDL- C results in a significantly lower mean levels of both S. Tes and S. SHBG. Obesity, among the other core

characteristics of MetS, seems to have the main suppressor effect on serum testosterone and SHBG in T2DM.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting from insulin deficiency or a defect in insulin action or a combination of both *(*European Society of Cardiology,2011). Diabetes mellitus is classified as either type 1 or insulin-dependent which can be controlled only by daily injections of insulin or type 2 or non-insulin dependent which is treated by several types of synthetic therapeutics. Type 2 DM significantly increases the risk of developing cardiovascular diseases such as coronary heart disease , stroke and amputation (Huang et al.,2007). Metabolic syndrome (MetS) is defined as an association of interrelated risk factors of metabolic origin such as obesity, dyslipidemia and hypertension with a heightened risk for cardiovascular disease in T2DM (Răzvan 2011, Sattar *et al.*, 2003). The prevalence of the metabolic syndrome in patients with type 2 diabetes mellitus varies between 70-90 % (Alexander,2003; Isomaa,2001; Song,2008).

Testosterone is a steroid hormone and is the primary mammalian androgen and is produced primarily by the testes, but also in small quantities by the adrenal glands in both males and females *(Carlson, 2003*). In the circulation, testosterone is bound with high affinity to sex hormone-binding globulin (SHBG) and weakly to albumin while there is a small fraction of unbound or free testosterone (Kaufman and Vermeulen,2005).

Prolactin is 199-amino acid single polypeptide chain with very similar structure to that of Growth hormone (GH) and human placental lactogen (HLP) (Moustafa *et al*.,2008). It is mainly produced by lactotropes ,which normally comprise about 15-25%

of the anterior pituitary (adenohypophysis) (Scully and Rosenfled ,2002) and it is also produced by some immune cells especially lymphocytes.

Testosterone levels in men with diabetes were described to be lower compared to men without a history of diabetes (Stanworth and Jones,2009, Stanworth *et al.*,2009). There are epidemiological evidences that low testosterone level is an independent risk factor for the development of both the metabolic syndrome *(Chubb and et al,2008)* and type 2 diabetes in later life (Stanworth and Jones,2009, Traish *et al.*,2009). Some studies have debated that metabolic

syndrome may suppress circulating testosterone levels or that low testosterone induces the metabolic syndrome (Laaksonen *et al.*,2004; Stellato *et al.*,2000). Some other studies have demonstrated that men with type 2 diabetes have lower testosterone levels than weight-matched non diabetic control subjects (Barrett-Connor ,1992; Tibblin *et al.*,1996).

Dyslipidemia is a term that is commonly used to describe the presence of an increased serum TG level and /or decreased serum HDL level (ADA,2012)

Characteristics of Metabolic Syndrome:

1.Hypertension (HT): Blood pressure measurement is higher than 140 /90 or the patient was on regular treatment with anti-hypertensive treatment (Alberti and Zimmet,1998)

2.Obesity: A patient with BMI >30 was considered as obese (Alberti and Zimmet,1998)

3. Serum Triglycerides level(TG): TG level >150 mg/dl was considered abnormal (ADA,2003).

4. Serum high density lipoprotein cholesterol (HDL-C): HDL-C level < 40mg/dl was considered abnormal (ADA,2003).

Material and Methods

The study was conducted at Department of Physiology, College of Sciences , Wasit University and the Clinics of diabetes mellitus at Al- Zahra Teaching Hospital and of Al – Karama Teaching Hospital, City of Kut, Iraq during the period from February 2011 to August 2011. One hundred and sixty patients attending these clinics and have type 2 diabetes mellitus were enrolled in this study. Their mean age was (49.8 ±5.7) years and the duration of their disease ranged from (1-35) years .

Medical Examination

Medical history was taken by personal interviewing with the help of a printed questionnaire. All measurements were undertaken by the same examiner. Exclusion was made for those who had a concurrent acute illness or another major systematic diseases except hypertension. Also patients who were taking a lipid lowering agent or were smokers were excluded. The following clinical characteristics were reported:

1. Age and gender
2. Weight and height in order to calculate body mass index(BMI)
3. Blood pressure measurement or a history of hypertension.

Laboratory analyses:

Specimen:

Subjects were asked to fast for 12 h before blood sampling, which was done between 8:00 and 9:00 A.M. Serum was collected for estimation of triglycerides and HDL-C on the same day of the visit of the patient.

Lipid profile assay:

Serum total cholesterol and triglyceride level were determined by totally enzymatic methods (Human company, Germany). Estimation of serum HDL-C was done by precipitation phosphotungstate-$MgCl_2$ solution followed by enzymetic determination of cholesterol in the supernatant (BioMeriuxe (France). LDL-C was calculated according to Friedwauld's formula (Friedwauld, etal., 1972)

Hormonal assay

The assay of serum testostertone, and prolactine was done by ELISA kits supplied by Hnuma company, Germany while the assay of serum SHBG was done by ELISA kits supplied by Kiel company, Germany.

Statistical analysis:

Data were presented in simple statistical measures of number, percentage, mean and standard deviation. Statistical analysis was done by using student s t- test for the significance of difference of quantitative data between two mean values .A probability value ($p<0.05$) was considered to be statistically significant .

Results

1.Personal characteristics of study groups:

The personal characteristics included the main traditional risk factors for T2DM.The mean value of body mass index (BMI) for study group was within the range of either overweight or obese class (29.10 ± 4.23) (Table 1).The mean value of HbA_{1C} ratio for study group was higher than normal (9.4 ± 2.1 %).

2. Biochemical analytes:

2.1 Lipid profile

Table (1) also shows the mean values of biochemical analytes of study groups. It included the components of lipid profile of the study groups. The mean level of serum total cholesterol in study group was (189.1 ±37.5 mg /dl), of total triglycerides was (143.8 ±56.3), of high density lipoprotein –cholesterol was 43.0 ±10.2 mg/dl , and of low density lipoprotein –cholesterol was (117.3±31.8 mg / dl) respectively.

2.2 Hormonal profile

The mean values of hormonal analytes of the study patients are shown in table (1). The mean level of serum testosterone was (4.49 ±2.11 ng/ ml), of sex hormone binding globulin was (11.22±9.42 ng/ ml), and of prolactin was(28.88±18.12 ng/ ml) respectively.

3. Hormonal profile of type 2 diabetic patients according to the resence or absence of a metabolic characteristic:

Type 2 diabetic disease patients were classified according to the presence or absence of a certain characteristic of metabolic syndrome in Table 4 and as follows :

Hypertension: No significant differences in the mean of serum testosterone ,SHBG, and prolactin were detected between normotensive and hypertensive diabetic patients (Table 2).

Obesity: A significant difference in testosterone level between non obese and obese diabetic patients was revealed ($P < 0.001$) while no significant differences in the mean level of serum SHBG and prolactin were observed.

TG: No significant differences in the mean levels of serum testosterone ,SHBG, and prolactin were detected between normal serum TG and abnormal serum TG groups of diabetic patient (Table 2).

HDL-C: No significant differences in the mean levels of serum testosterone , SHBG, and prolactin were detected between groups of normal and abnormal serum HDL-C (Table 2).

4. Factors of dyslipidemia in type 2 diabetic patients according to presence or absence of a certain metabolic characteristic

(Table 3) shows the analytes of dyslipidemia in type 2 diabetic patients compared according to the presence or absence of a certain metabolic characteristic.There was a significant decrease in HDL-C level in obese compared to non obese diabetic patients.

5. Hormonal profile of type 2 diabetic patients according to accumulation of defined metabolic characteristics

In table (4), sex hormone profile of type 2 diabetic patients was analyzed according to accumulation of metabolic characteristics (Diabetic plus hypertension with or without obesity and dyslipidemia). In the presence of hypertension and obesity in diabetics, the SHBG level was significantly increased in comparison with diabetics who were hypertensive non obese patients (25.16±13.42 vs. 33.58±13.73 respectively , $P < 0.05$).

In the presence of hypertension , obese and lower HDL-C then diabetics had SHBG and testosterone levels that were significantly decreased in comparison with diabetics who were hypertensive, obese with higher (or normal) HDL-C level (30.63±14.93 vs. 40.7± 6.33 and 3.73±1.9 vs. 5.57±1.53 respectively , $P<0.01$) (Table 4) .

6. Correlations between measures of hormonal profile of study group (type 2 diabetic patients)

Table 5 showed a highly significant correlation between testosterone and SHBG in study group ($r = 0.407$, $P < 0.01$) while no significant correlation was found between SHBG and prolactin (Table 5).

Table 1: Personal characteristics and biochemical analytes of study patients

Characteristic or analyte	Range	Mean ± SD (N= 160)
Age (year)	40-55	49.8 ±5.7
Duration of DM (year)	1-24	5.4 ±5.2
BMI	19.39 - 42.70	29.10 ±4.23
Fasting serum sugar (mg / dl)	81 - 419	200.9 ±75.2
HbA_{1c} (%)	4.2 - 15.6	9.4 ±2.1

TC (mg/dl)	97.2 - 286	189.1± 37.5
TG (mg/dl)	53.8 - 212.1	143.8± 56.3
HDL-C (mg/dl)	25.6 – 70.3	43.0± 10.2
LDL-C (mg/dl)	83.2 - 209.4	117.3± 31.8
Testosterone ng/ml	1-12.22	4.49±2.11
Sex hormone binding – globulin (ng/ml)	0.12-141.93	28.88±18.12
Prolactin (ng/ml)	1.3-45.55	11.22±9.42

N : number ,SD : standard deviation TC = Total cholesterol, TG = Triglycerides, HDL-C = High Density Lipoprotein-cholesterol ,LDL-C = low Density Lipoprotein-cholesterol

Table 2 : Hormonal profile of type 2 diabetic patients according to the presence or absence of a metabolic characteristic

Metabolic characteristic (Total N= 160)		Number (Percent %)	Testosterone (Mean±SD)	SHBG (Mean±SD)	Prolactin (Mean±SD)
Hypertensio	Normotensiv	90 (56.3)	4.46±2.22	27.94±20.73	10.55±9.78
	Hypertensive	70 (43.7)	4.53±1.97	30.08±14.13	12.07±8.92
BMI	Non Obese	89 (55.6)	4.79±2.17	29.03±20.99	10.99±9.32
	Obese	71 (44.4)	3.89±1.87** P<0.001	28.69±13.85	11.5±9.58

N :

TG	Normal	35 (21.9)	4.35±1.7	26.43±13	12.61±9.52
	Abnormal	125 (78.1)	4.53±2.21	29.57±19.3	10.83±9.39
HDL-C	Normal	107 (66.9)	4.3±2.9	27.94±17.91	10.38±9.37
	Abnormal	53 (33.1)	4.88±2.09	30.78±18.58	12.91±9.37

number, SD: standard deviation,**: Highly significant

Table 3:Factors of dyslipidemia in type 2 diabetic patients according to presence or absence of a certain metabolic characteristic

N :

Metabolic characteristic (Total N= 160)		Number (Percen %)	TG (Mean±SD) mg /dl	HDL-C (Mean±SD) mg/dl
Hypertension	Normotensive	90 (56.3)	139.95±54.88	43.63±10.86
	Hypertensive	70 (43.7)	148.74±57.99	42.28±9.63
BMI	Non Obese	89 (55.6)	141±57.08	45.14±11.39
	Obese	71 (44.4)	147.31±55.4	40.41±7.89** P<0.01

number ,SD: standard deviation ,**: Highly significant

Table 4: Hormonal profile of type 2 diabetic patients according to accumulation of defined metabolic characteristics

Metabolic characteristic (Total N= 160)		Testosterone (Mean±SD) ng/ml	SHBG (Mean±SD) ng/ml	Prolactin (Mean±SD) ng/ml
Diabetic N= 160	Normotensive N=90	4.46±2.22	27.94±20.73	10.55±9.78
	Hypertensive N=70	4.53±1.97	30.08±14.13	12.07±8.92
Diabetic+ Hypertensive N= 70	Non obese N=29	4.91±1.94	33.58±13.73	11.65±9.83

	Obese N=41	4.27±1.97	25.16±13.42* P<0.05	12.38±8.32
Diabetic+ Hypertensive+ Obese N=41	Normal TG N=8	4.46±2.18	36.06±11.59	12.38±8.32
	Abnormal TG N=33	4.22±1.96	32.97±14.29	12.37±6
	Normal HDL-C N=29	5.57±1.53	40.7±6.33	12.33±9.19
	Abnormal HDL-C N=12	3.73±1.9** P<0.01	30.63±14.93** P<0.01	12.49±6.08

N : number
SD: standard deviation
* : Significant
** : Highly significant

Table 5: Correlations between measures of hormonal profile of study group (type 2 diabetic patients)

	SHBG	Prolactin
Testosterone	0.407**	0.001
SHBG	1	0.019

**: Highly significant

Discussion

This study has analyzed the association between components of metabolic syndrome and sex hormone profile of T2DM diabetic patients in whom MetS is prevalent (Saad and. Gooren,2009). In analyzing each component separately, our study has shown that obese diabetics had a significantly lower serum testosterone level than in non obese diabetics. Such an association has been detected in other studies (Svartberg *et al.*,2004; Atlantis *et al.*,2009; Barrett ,*1992*; Khaw and Barrett, 1992).

In recent years, it has been demonstrated that the fat cell functions as an endocrine cell that produces and secretes molecules with regulatory potential called cytokines / adipokines, of which leptin is one prominent representative. In men, there appears to be a correlation between body mass index or the fat mass on one hand and leptin levels on the other. Leptin may be a factor in the association between adiposity and decreased testosterone levels. Leptin receptors are present on Leydig's cells and inhibit the testosterone generated by administration of human chorionic gonadotropin (Isidori *et al.*,1999). Visceral obesity with its associated hyperinsulinism suppresses

SHBG synthesis and circulating testosterone plasma levels (Armin ,2008). Moreover, in obese men, there is an attenuated pulse amplitude of luteinizing hormone (LH) while the LH pulse frequency is unaffected, thus producing a weaker stimulation of testicular testosterone production (Lima *et al.*,2000, Vermeulen et al., 1993).

It has also been suggested that the increase in adipose tissue mass in obesity may result in increased aromatase activity and thus lead to a greater conversion of testosterone into estradiol (Giagulli *et al*.,1994). An increase in estradiol concentrations would lead to the suppression of hypothalamic gonadotropin- releasing hormone and pituitary gonadotropin secretion. This would result in the reduction of both testosterone secretion by Leydig's cells and spermatogenesis in the seminiferous tubules. On statistical analysis, obesity by itself exerted no significant effect on SHBG but a significant decrease was shown if hypertension was present as well. Many other reports have showed an association between SHBG and obesity alone (Jang *et al;*2011, Samah,2003, Armin , 2008).

In this study , serum HDL level was significantly lower in obese compared with non obese diabetics. This is consistent with many other reports (Kolovou *et al*.,2005; Ginsberg and , Huang,2000). Also there was no significant difference in testosterone level between normal HDL-C and abnormal HDL-C but the difference was apparent and was significant in the presence of hypertension and obesity. In this analysis , HDL-C level by itself showed no significant association with testosterone but a highly significant decrease was shown if hypertension and obesity were present as well. This is consistent with other reports that showed an association between HDL-C and testosterone (Barrett ,1992; Khaw and Barrett, 1992). Moreover, our study has detected a significant association between HDL-C and obesity. Thus, our results go with the definition of metabolic *syndrome (Meigs et al.*,2006; Malik *et al.*,2005).

In this analysis , HDL-C by itself exerted no significant effect on SHBG but a significant decrease was shown if hypertension and obesity were present as well. This is consistent with other reports that showed an association between HDL-C and SHBG (Goodman *et al ,1996;* Tchernof *et al.,1995).*

In this analysis ,SHBG was a highly significant correlation with testosterone . This is in agreement with the finding reported by many studies (Onat *et al.*,2007; Jang *et al.*2011)and is related to the fact that SHBG is the main carrier of testosterone in blood*(Torkel et al.,2009;* Paul *et al.*,2008).

In Conclusion: Our T2DM patients have a bad glycemic state and are characterized by a significantly lower S. Tes mean level if they were obese. Still, the accumulation of other core characteristics of MetS which includes hypertension and lower S. HDL- C results in a significantly lower mean levels of both S. Tes and S. SHBG. Obesity, among the other core characteristics of MetS, seems to have the main suppressor effect on serum testosterone and SHBG in T2DM

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