Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-nahrain.edu.iq

Gonadal Dysfunction with Postprandial Hypertriglyceridemia is Risk Predictor of Cardiovascular Disease in Men with Type 2 Diabetes Mellitus

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Abstract

Background The association of type 2 diabetes mellitus and risk of cardiovascular disease is well documented. Insulin resistance is the hallmark feature of type 2 diabetes and there is evidence to suggest that testosterone is an important regulator of insulin sensitivity in men, with a role for testosterone in lipid metabolism and specially the triglyceride fraction.

Objective To emphasize the association of low level of total testosterone with that of the postprandial triglyceride in male patients' with type 2 diabetes mellitus.

Methods Forty two type 2 diabetes mellitus male patients and 42 healthy controls of age range between 30-60 years**,** during the period from December 2011 to June 2012. Postprandial venous blood used for random blood glucose, lipid profile, urea and creatinine measurement. Luteinizing hormone, follicle stimulating hormone, testosterone, and sex hormone binding globulin was done using Enzyme-Linked Immuno Sorbent Assay (Sandwich assay).

Results A negative correlation between testosterone, and postprandial triglyceride, in both type 2 diabetes mellitus and control groups with a significant difference in testosterone between the two groups. The sex hormone binding globulin was also correlated negatively with postprandial triglyceride in only the control group.

Conclusion Hypogonodism in male (decline in testosterone level) leads to increased postprandial hypertriglyceridemia, which could, both, be considered of predictors for cardiovascular disease risk factors in male patients with type2 diabetes mellitus.

Key words Postprandial triglycerides, type2 diabetes mellitus, testosterone.

Introduction

Dyslipidemia caused by insulin resistance is characterized by hyper-triglyceridemia with low HDL-cholesterol (HDL-c), two important risk factors for the development of diabetes mellitus [(1,2)]. Testosterone was reported to have important metabolic actions in men, affecting body composition and exerting direct effects on insulin sensitivity and lipid metabolism [(3,4)]. Hypogonadism is either primary or secondary. Hypogonadism that accompanies most chronic systemic diseases and aging is primary and is characterized by low testosterone levels and high gonadotropin with a significant association with insulin resistance and development of diabetes mellitus. The low level of sex hormone binding globulin (SHBG), which associates low testosterone concentration, has also been considered a risk predictor of Type 2 DM; prospective studies have shown that men with higher testosterone levels had a 42% lower risk of type 2 diabetes [(5-9)]. The Massachusetts

Male Aging Study (MMAS) and the Multiple Risk Factor Intervention Trial (MRFIT) have shown that low levels of total testosterone and SHBG (which is associated with insulin resistance) were both independent risk factors in middle-aged men who later developed diabetes [10,11]. The present study was undertaken to emphasize the relationship between serum testosterone levels and postprandial hypertriglyceridemia, on one hand, and their relation to the development of cardiovascular disease (CVD) risk in male diabetic patients, on the other.

Methods

This study included 42 male patients with T_2DM of age ranged between 30-60 years and disease duration of 1-8 years, who were attending the Diabetic Clinic at Al-Kadhimyia Teaching Hospital, during the period from December 2011 to June 2012. The study also included 42 normal male volunteers matching in their age and body mass index (BMI) with the patient group. Type 1 DM and thyroid disease patients were excluded from the study.

Ten ml were withdrawn from each patient and control subject between 2-4 hours after meal (postprandial state for lipid test) in a plain tube and centrifuged for 15 minutes at 3000 rpm after being allowed to clot at room temperature for 30 minutes. The separated sera were divided into aliquots and stored frozen at -20^{o}C, and then used for measurement of hormones. Random blood glucose, postprandial lipid profile, urea and creatinine were done immediately after separation of the serum using the available routine methods. The determination of patients' sex hormones (leutinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and SHBG) was done by Sandwich Enzyme-Linked Immuno Sorbent Assay (ELISA assay). The oral consent had been taken from all patients and controls for blood collection.

Statistical analysis

All values were expressed as mean ± standard deviation (mean ± SD). All Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS version 15.0). Independent student t-test was performed to assess differences between two means. Pearson correlation coefficient was used to determine the correlation between quantitative data. *P* value < 0.05 was considered significant [12].

Results

Table 1 shows significant differences in the mean ± SD values between the diabetic and control groups in testosterone, SHBG ($P < 0.001$; $P < 0.004$, respectively) and in LH ($P < 0.0001$), while there was no significant differences in mean values of FSH.

There is also significant differences in the mean ± SD values of glucose, TG, T-cholesterol, HDL-c ($P < 0.0001$); LDL ($P = 0.0002$) and atherogenic index $P = 0.0004$, while no significant differences in the mean values of age, BMI, urea and creatinine there were observed. In both control and patient groups serum testosterone showed inverse correlations with the postprandial TG (Figs. 1 and 2).

Discussion

The lower serum testosterone and SHBG in the present diabetic patients confirm previous studies, which have suggested a role for low androgenic activity in the development of obesity, insulin resistance and Type 2 DM in men [13-17]. Obesity is a factor, which complicates the picture of Type 2 DM. The hypothesis of hypogonadal-obesity cycle originally suggested by Cohen in 1999 stated that testosterone inhibits adipocytes lipoprotein lipase activity [18]. In cases of low testosterone, which may result from increased aromatase activity, there is an increase in the adiposity and fat deposition which may cause a decline in testosterone level. The lower SHBG in the sera of the present diabetics could be attributed to high insulin levels which decrease the release of SHBG from hepatocytes [19,20]. However, other reports attributed this decline in SHBG to high glucose or fructose concentrations, which suppress its expression in the hepatocytes [21]. The impairment in the feedback inhibition, which is normally present between testosterone and LH, is the cause of high serum LH in the present diabetics [22].

Table 1. Demographic parameters of the diabetic patients and the control group

Parameters	Diabetic Patients N = 42	Control Group N = 42	*P* value
Age (yr)	48.88 ± 8.73	45.55 ± 7.05	0.0576
BMI (kg/m^2)	31.07 ± 5.26	30.4 ± 5.28	0.5635
Glucose (mmol/l)	12.46 ± 5.12	5.5 ± 1.24	<0.0001
TG (mmol/l)	2.71 ± 0.89	1.77 ± 0.53	<0.0001
Tc (mmol/l)	5.63 ± 0.73	4.46 ± 0.74	<0.0001
HDL-c (mmol/l)	0.92 ± 0.2	1.15 ± 0.2	<0.0001
LDL-c (mmol/l)	3.49 ± 0.71	2.43 ± 0.69	0.0002
Atherogenic index	3.98 ± 1.35	2.23 ± 0.87	0.0004
Urea (mmol/l)	5.93 ± 0.94	5.97 ± 0.67	0.8462
Creatinine (µmol/l)	75.48 ± 7.51	74.1 ± 7.7	0.4068
FSH (IU/l)	9.3 ± 6.67	7.71 ± 5.66	0.242
LH (IU/l)	7.81 ± 2.46	5.62 ± 2.02	<0.0001
Testosterone (nmol/l)	11.38 ± 3.8	14.62 ± 5.04	0.0013
SHBG (nmol/l)	24.31 ± 13.53	33.67 ± 16.01	0.0049

BMI = Body Mass Index, TG = Triglycerides, Tc = Total Cholesterol, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, FSH = Follicular stimulating hormone, LH = luteinizing hormone, SHBG = sex hormone binding globulin

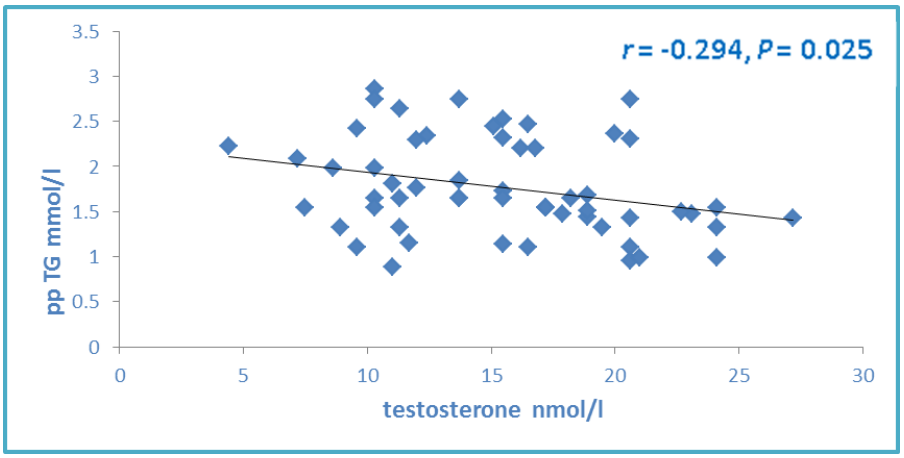

Fig. 1. Correlation between testosterone and postprandial triglycerides in the control group

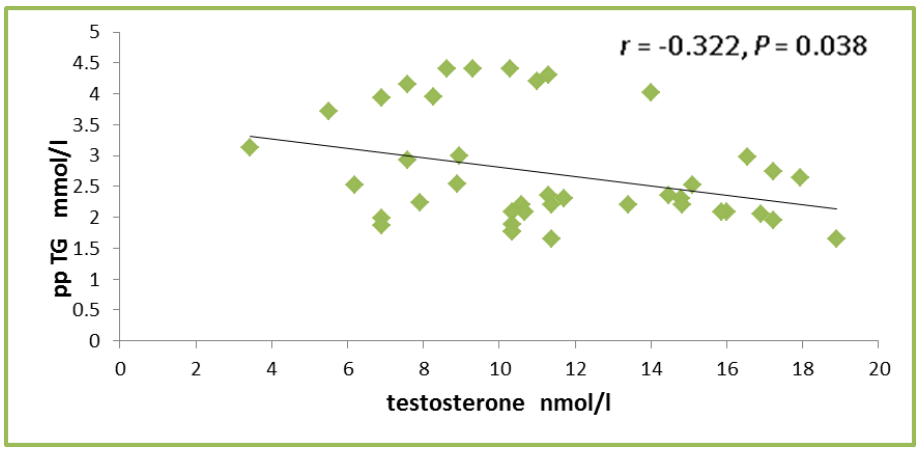

Fig. 2. Correlation between testosterone and postprandial triglycerides in diabetic patients

Also In control group of this research there was significantly negative correlations between post prandial (pp) TG with testosterone as in figure 1. This consider as risk factor for developing many systematic disease e.g. Type 2 DM and CVD in which the dyslipidemia is the main characteristic feature, and this agreed with Iraqi clinical study [23].

Elevated serum triglyceride level is a common dyslipidemic feature that accompanies Type 2 DM and pre-diabetic states [24], a picture which can be seen better with the postprandial TG than the fasting TG [25]. This point clarifies the reason for using the postprandial TG in many of the recent reports on DM or CVD [23,26-28]. Elevated levels of postprandial TG indicate the presence of increased levels of remnants from chylomicrons and very LDL-c. The cholesterol-containing, triglyceride-rich lipoproteins penetrate the arterial endothelium and may get trapped within the sub-endothelial space, potentially leading to the development of atherosclerosis [29].

The rise of this predictor pp TG of atherosclerosis risk associates the decline in serum testosterone level in the present diabetics and their control which implies the importance of both factors in this respect and necessitates their improvement to decrease the risk of atherosclerosis and CVD.

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Received 7th Jan. 2013: 15th Mar. 2013.