Original paper

Impact of Excess Androgenic Activity on Non-Fasting Serum Lipid Profile in Reproductive Age Women with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is an endocrinopathy that affects people of different ages. It is among the components of metabolic syndrome which has broad health implications. Obesity, insulin resistance and hyperandrogenism coexist in T2DM, and could have independent and interactive effects on dyslipidemia manifested mostly by elevated low-density lipoprotein cholesterol (LDLc), triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDLc).

Aim of the study was to confirm the relationship between non-fasting TG, testosterone (Ts) and sex hormone binding globulin (SHBG) levels in reproductive age women with T2DM.

Materials and Methods: Serum non-fasting lipid profile and sex hormone levels were measured in 40 female patients with T2DM and 35 normoglycemic women without a known family history of diabetes mellitus as a control group.

Enzymatic colorimetric methods were used to measure the non-fasting lipids and blood glucose, while Eliza technique was used to measure testosterone (Ts) and sex hormone binding globulin (SHBG) by DRG-ELISA kit.

Results & Discussion: There are significant elevations in triglycerides (TG) and atherogenic index (AI), with highly significant reduction in HDL-C, $p< 0.001$; in the patient group (women with T2DM) as compared to their control group .There were no significant differences in the mean total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C).

As concerning sex hormones, there was a significant reduction in SHBG concentrations ($p< 0.01$) in T2DM women in relation to their normal glycemic control women. Serum total Ts levels showed no marked difference between the two groups, however it showed a significant correlation with the TG ($p< 0.05$) and AI ($p <0.05$) in the T2DM women. The free androgenic index (FAI) was significantly higher in the T2DM group and showed a significant correlation with serum TG.

Conclusion: These results confirm the association of low SHBG with elevation in androgenic activity and non-fasting TG in the diabetic women with expectation of high risk of cardiovascular disease.

Keywords: type 2 diabetes mellitus, non-fasting lipid profile, Testosterone, Sex hormone binding globulin and free androgenic index

Introduction

An important feature of T2DM is insulin resistance to which many of the diabetic events were referred [(1)]. Hyperinsulinemia in women was reported to increase ovarian testosterone secretion and reduce hepatic Sex hormone binding globulin (SHBG) synthesis [(2, 3)] with a consequent increase in free androgenic activity (FAI), which

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would increase TG concentration and reduce HDL cholestesterol [4]. However different reports gave different results for the relation between hyperandrogenicity and changes lipid profile [5].

Berger et al. in 2012 [6] reported a significant association of serum TG , VLDL particles size and intermediate density lipoprotein (IDL) with incident ischemic stroke in postmenopausal women, while more recent report considered raised TG and TG-rich lipoproteins as additional cause for cardiovascular disease [7]

Focusing on non-fasting lipids came from many workers during this decade who found that elevated concentration of non-fasting TG is a better indicative risk factor for incident cardiovascular disease or stroke than fasting TG. [7, 8, 9, 10]

The present work was undertaken to determine the relation between SHBG, hyperandrogenism and elevated non-fasting TG in reproductive age women with T2DM, factors which may increase the risk for cardiovascular disease.

Materials and Methods

Forty women with T2DM aged between 25-39 years, with a mean of 30 ±7.2 (± SD) years, were recruited from High Institute for Infertility Diagnosis & Assisted Reproductive Technologies, Baghdad -Iraq. The study was conducted during April to July 2012.

Another 35 apparently healthy women were involved as a control group with a mean age of 25 ± 6.54 (±SD). None of them had a history of thyroid disease, polycystic ovary syndrome, diabetes mellitus, renal impairment, or any other severe illness or infection, and not taking any drug (including hormone replacement and any estrogenic, antihypertensive or lipid lowering medication) or had any operation on the ovary.

Blood collection:-

Ten mls of blood were collected into a plain test tube from both groups in the non-fasting state (2-3 hours after breakfast) in the morning. The serum was obtained after centrifugation at 3200 rpm for 10 min. and divided into small aliquots for:

a- Immediate measurement of serum glucose, lipid profile, by enzymatic colorimetric methods. Atherogenic index (AI) is the ratio between LDL-c to HDL-c.

b- The rest was stored at (-20 C°) until assayed for hormones: total testosterone (TTs) and SHBG by DRG- ELISA kit. free androgen index (FAI) =TTs (nmol/ L)) x 100/SHBG) (nmol/ L)).

Results

As shown in table 1, the non-fasting TG, and AI were significantly higher in the T2DM women with a marked reduction in HDL-c, while there was no significant differences in serum total cholesterol and LDL-c levels between both T2DM patients and their control group.

There was, also, low serum SHBG in the T2DM patients relative to the normal controls, with no significant change in serum TTs, however it was positively correlated with both TG and AI (figs.1 ,2) . The FAI was significantly higher in the T2DM women and positively correlated with serum TG (fig.3).

Discussion

A very early study on the role of sex hormones in dyslipidemia showed an increase in LDL-c and a decrease in HDL-c upon administration of exogenous androgen to premenopausal women which implied the involvement of these hormones in the risk of cardiovascular disease ([11]).

The importance of SHBG role in this respect comes from its effect on the ratio between free testosterone (FT) and bound testosterone (BT) and other androgens [12].

Table 1. Comparison between T2DM women and their controls:

parameters	T2DM (mean ±SD) (n=40)	controls (mean ±SD) (n=35)
Age(year)	27±9.3	28±6.54
FBG (mmol/L)	9.52±1.4	4.32±0.31
TG (mmol/L)	2.84±0.66***	1.81±0.74
TC(mmol/L)	4.13±0.76	4.53±0.81
HDL-C (mmol/l	0.71± 0.09***	1.18±0.28
LDL-C (mmol/L	3.31±0.77	2.52± 0.85
AI	4.76±1.30***	2.27±0.97
TTs (nmol/l)	1.48±0.54	1.23±0.53
SHBG (nmol/l)	54.10±8.65***	80.13±15.67
FAI	2.71±0.86***	1.74±0.55

P* = 0.05, p**= 0.0005, p***= 0.0001

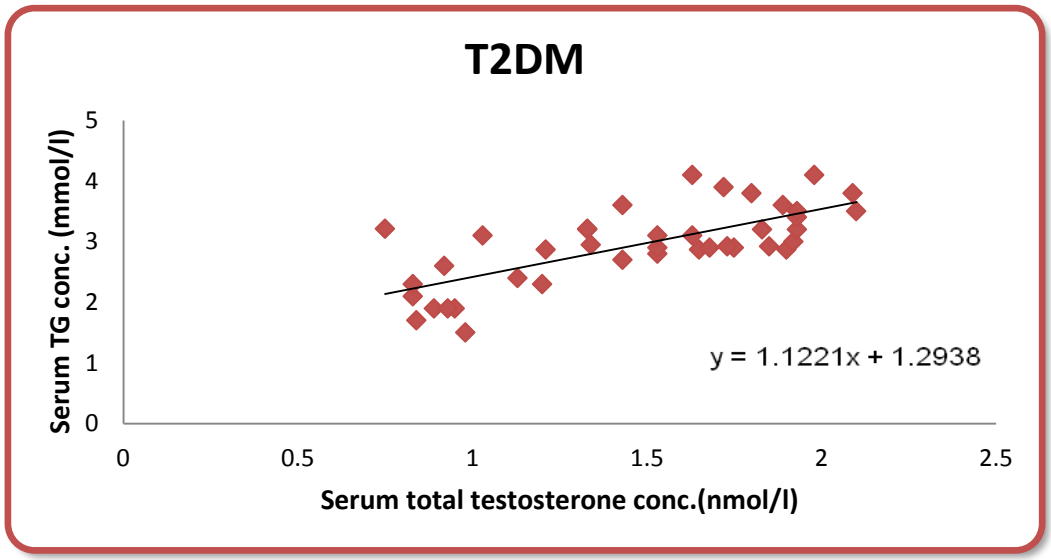

Figure 1. Correlation between serum total testosterone concentration and non-fasting triglycerides in type2 Diabetes Mellitus patients(r =0.72, p < 0.05, n = 40)

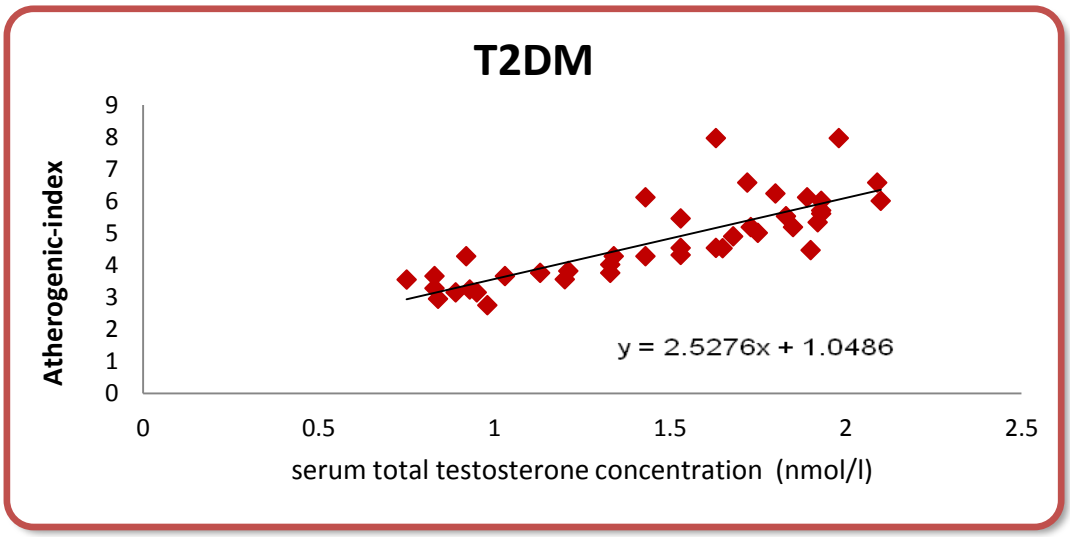

Figure 2. Correlation between serum total testosterone concentration and atherogenic index in type2 diabetic women (r= 0.8, p < 0.05, n=40)

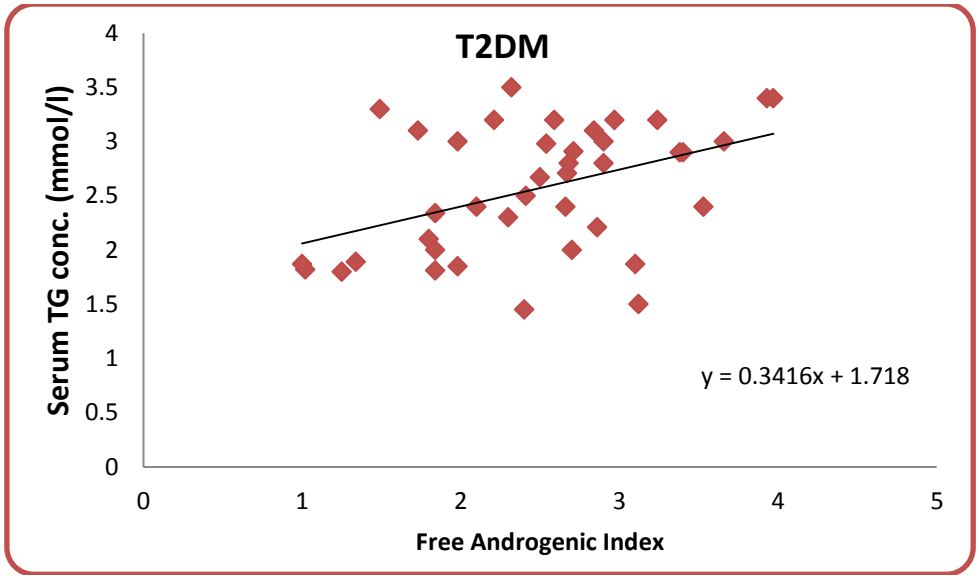

Figure 3. Correlation between non-fasting serum triglyceride and free androgenic index in the type 2 diabetic women. (r =0.438, p < 0.05, n = 40)

The association between FT and BT with insulin resistance and other related diabetic events were found to be valid after adjustment for obesity [13, 14], however some other workers failed to show this independent association in pre or post-menopausal women [15, 16]

On the other hand, low SHBG was found to increase TG and decrease HDL-c in 777 randomly selected males and females [17]. Direct regulatory effect on hepatic and lipoprotein lipases by Ts and SHBG has been suggested by some reports [18] .These two lipases are considered key enzymes for regulation of TG and HDL-c levels. The hepatic lipase is stimulated by testosterone and results in increased TG and decreased HDL-c. On contrast SHBG stimulates lipoprotein lipase resulting in increased clearance of circulating TG, hence lowering of TG level. This may explain the higher levels of serum TG which associated low SHBG and high FAI in the T2DM women of this study. However, the reports about the relation between androgen levels and atherogenesis are contradictory. It was postulated that very high androgenicity only would induce atherogenesis [5].

Low levels of SHBG in diabetes mellitus has been reported by many workers and led to the conclusion that changes in this hormone could be considered as one of the genetic and environmental factors that may lead to the events of diabetes mellitus [19]. Its role as a risk for T2DM could come from the transmission in one of the polymorphisms of SHBG gene which is believed to have such risk, and was even considered an independent risk predictor for T2DM.[20]

As concerning serum TTs level, which showed no significant changes from the control, it is possible that the ratio between FT and BT has changed by low SHBG since testosterone has a high affinity to bind to SHBG [21]. Unfortunately we did not measure FT in this study.

Conclusion

In conclusion it could be said that low SHBG may be the trigger for hyperandrogenism and hypertrigly-ceridemia in T2DM which would increase the risk for cardiovascular disease or stroke, and that monitoring SHBG and non-fasting TG levels in women, in general, and in those with T2DM, in particular, is essential.

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