

Postprandial hypertriglyceridemia and androgen dysfunction relationship in men with end stage renal disease

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Abstract:

Background: Gonadal function is affected with end stage renal disease. In men the disturbances of the hypothalamic–pituitary–testicular axis can be detected with only moderate reductions in the glomerular filtration rate. There are many evidences that confirm the effect of testosterone on lipid metabolism in postprandial state.

Objective: to study the relationship between low level of total testosterone and postprandial lipids in male patients with end stage renal disease.

Subjects & Method: the study involved 38 male patients with end stage renal disease (age range of 30- 60 years) attending the unit of kidney disease and transplantation at Baghdad Teaching Hospital , and 35 healthy subjects (control group) of matching age and weight during the period from January to march 2013. Postprandial venous blood was obtained for glucose, lipid profile, urea and creatinine measurement immediately after separation of the serum by routine colorimetric methods .

The determination of androgen sex hormones (luteinizing hormone , follicle stimulating hormone , testosterone , and sex hormone binding globulin .) was done using Enzyme-Linked Immuno Sorbent Assay. (Sandwich assay).

Results: There was a significant negative correlation between free testosterone, and postprandial triglyceride in both ESRD patients and control groups with a significant difference in testosterone between these two groups. The sex hormone binding globulin was also correlated negatively with postprandial triglyceride in the control group.

Conclusion: Decline in free testosterone level associated increased postprandial hypertriglyceridemia, which could, both, be considered predictors for cardiovascular disease risk factors in male patients with ESRD.

Key words : *Postprandial hypertriglyceridemia , free testosterone, androgen dysfunction ,ESRD.*

Introduction:

Chronic kidney disease is a progressive loss in renal function over a period of months or years. There are no specific symptoms of deterioration of kidney function. A reduced appetite and feeling unwell might be the main symptoms of kidney dysfunction. Diabetes and /or high blood pressure are the main risk factors for development of kidney problems . Chronic kidney disease was classified in five stages begin with stage 1, with mildest and causing few symptoms which progressed to severe illness with poor life expectancy in stage 5 if untreated. This is according to the professional guidelines classification. Creatinine levels may be normal in the early stages of CKD, and the condition is discovered if urinalysis shows that the kidney is allowing the loss of protein or red blood cells into the urine (Levin et al 2008). Eventually, kidney failure (stage 5 CKD) ensues and kidney replacement therapy is required (NKF-KDOQI 2002 &Johnson 2011).

In CKD, the secretion of hormones and the response of target tissues were affected causing endocrine dysfunctions. As many as 50 to 70% of men with ESRD have been reported to be hypogonadal on the basis of low concentrations of total and free testosterone due to moderate reductions in the GFR which leads to an alterations of sex steroid production and metabolism (Karagiannis and Harsoulis 2005 & Albaaj et al 2006)

Dyslipidemia is one of the important clinical features in ESRD manifested by hyper-triglyceridemia, elevated level of very low density lipoprotein (VLDL), high plasma concentration of lipoprotein remnants, accumulation of oxidized lipids and lipoproteins, low plasma HDL, cholesterol concentration and impaired HDL maturation

and function, while serum cholesterol and LDL cholesterol values are frequently within or below the normal limits (Vaziri 2006). Many studies reported that low total testosterone level is associated with an adverse lipid profile, which were included high TG level and low HDL-C (Agledahl et al 2008 & Page et al 2008 & Makinen et al 2008).

The major finding of the recent study has shown that the administration of total testosterone has beneficial effects on dyslipidemia especially on TG level. Another important finding of this study was the young and middle-aged men with the lowest total testosterone concentrations, had the highest risk of incident dyslipidemia (Cornoldi et al 2010).

Subjects & Methods:

This study included 38 male patients with ESRD of age range between 30-60 years and disease duration from 2-19 months, who were attending kidney disease and transplantation at Baghdad Teaching Hospital during the period from January to March 2013. Patients with diabetes mellitus and thyroid disease were excluded from this study. This study also included 35 normal male volunteers of matching age and BMI who were nonsmokers; non-alcoholics and none had dyslipidemia as revealed from previous laboratory tests.

Ten milliliters (10ml) of venous blood were withdrawn in 3-4 hr. after meal from both patient and control group. Blood samples were collected in a plain tube and centrifuged for 15 minutes at 3000rpm after being allowed to clot at room temperature for 30 minutes. The separated serum was divided into aliquots and were stored frozen at (-20 °C) to be used later for estimation of androgen sex hormone, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, free testosterone, sex hormone binding globulin (SHBG) by Enzyme-Linked Immune Sorbent (ELISA, Sandwich Assay).

While glucose, lipid profile, urea and creatinine analysis all were done immediately after separation of the serum by the routine colorimetric methods. Body mass index was calculated as body weight (in Kg/Sq height (meter)). The oral consent had been taken from all patients and controls for blood collection.

Statistical study:

All results 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. Person correlation coefficient was used to determine the correlation between quantitative data. P value < 0.05 was considered significant (Elliott and Woodward 2007).

Results & Discussion;

As shown in table 1, there is significant differences in total testosterone, free testosterone, FSH, LH between two groups ($p < 0.0001$), while no significant differences in SHBG ($p > 0.05$) can be noted. All other parameters measured were significantly higher (including serum lipids, urea, and creatinine). In the present study, the results were represent clearly low serum total testosterone and free testosterone in the ESRD patients relative to the normal controls, and this was associated with higher rise in the serum postprandial triglycerides, while there was no significant differences in SHBG level between both ESRD patients and their control group. These results were confirmed by the result of Albaaj *et al* 2006, while another study, noted that concentration of SHBG was elevated (Albaaj *et al* 2006 & Al-Khallaf *et al* 2012). Male hypoandrogenism i.e. low testosterone is the most common gonadal dysfunction in men, mainly due to reduced prolactin clearance. A prolactin-induced inhibition of gonadotropin, is considered as one of the most important causes of testosterone deficiency, and has been reported to associate cardiovascular risk factors and mortality in CKD and uremic inhibition of LH signaling at the level of the Leydig cells (Gungor *et al* 2010). Yilmaz *et al* 2011 found that every nmol/L decrease in total testosterone concentration in male lead to increase in the percentage (Approximately 22%) of cardiovascular risk in the ESRD patients (Yilmaz *et al* 2011).

The results of many studies considered the low level of serum testosterone or free testosterone a consequence of the changes in gonadal steroid genesis and decreased in synthesis and secretion of testosterone follow the progression of CKD as a result of the hypothalamic-pituitary-testicular axis dysfunction (Gungor *et al* 2010 & Yilmaz *et al* 2011 & Carrero *et al* 2010).

In healthy adult male, testosterone plays important role in lipid metabolism. With the age progressing the testosterone level will start decrease which predicts the development of central obesity and accumulation of intra-abdominal fat (Allan and McLachlan 2010 & Brand *et al* 2011). According to the results of many studies which have considered that the metabolic influence of TG and triglyceride rich lipoprotein (TRL) remnants which comprise a heterogeneous group of apo B-containing lipoproteins, including chylomicrons, VLDLs and IDLs have direct relation to atherogenic state (López-Miranda *et al* 2004). The mechanisms of aging and death in humans were discussed in many studies and one of their possible explanations that there was negative influence of androgens on the lipid profile which is more pronounced in aging men (Kolovou *et al*

2011). One of these studies has attributed the increase in the HDL consumption to the stimulation of reverse cholesterol transport (Hersberger et al 2005).

This hypothesis was supported by Jones *et al.* 2011 in their recent study by a longer-term testosterone replacement therapy (TRT) demonstrating that after an initial fall in their serum concentrations, HDL-C levels returned to baseline levels after 12 month (Jones et al. 2011).

In end stage renal disease patients there is an increase in ppTG levels and abnormal prolongation of this increase (Montague and Murphy 2009 & Piecha et al 2009 & Attman and Samuelsson 2009). The disturbance of the clearance of Chylomicrons remnants may underlie this change. However, since Chylomicrons compete with TRL of hepatic origin for lipolysis by LPL, the postprandial increase in triglycerides in the circulation is worsened by TRL of hepatic origin (Kaysen 2009). ²Thus, the postprandial increase in TG involves not only the metabolism of Chylomicrons of intestinal origin but also the metabolism of TRL of hepatic origin (Saland and Ginsberg 2007).

The general mechanisms underlying the dyslipidemia of renal disease may be alteration in the metabolism of postprandial lipoproteins, alteration in the metabolism of other TRL, changes in the route of reverse cholesterol transport, structural changes of lipoproteins that mean HDL-C undergoes structural changes through the incorporation of serum amyloid A, resulting in the so-called acute phase or inflammatory HDL, which act not as protective particles, but as pro-atherogenic particles (Saland and Ginsberg 2007 & Kwan et al 2007 & Perrea et al 2008). In chronic kidney disease there is an increase in pp TG levels and abnormal prolongation of this increase (Perrea et al 2008 & Badiou et al 2009 & Mesquita et al 2010).

The clearance of Chylomicrons remnants disturbed. However, since Chylomicrons compete with TRL of hepatic origin for lipolysis by LPL, Thus, the postprandial increase in TG involves not only the metabolism of Chylomicrons of intestinal origin but also the metabolism of TRL of hepatic origin (Mesquita et al 2010). Supportive observational studies have identified pp TG levels to be a superior predictor of CVD risk compared with fasting levels (Mesquita et al 2010 & Nordestgaard et al 2010). An inverse correlation between testosterone and each of ESRD, BMI, total cholesterol and TG was reported (Gungor et al 2010).

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Tables:

Table (1):- comparison between ESRD patients and their controls:

| Parameters | ESRD (mean \pm SD) (n=38) | Control(mean \pm SD) (n=35) |
|--------------------------------|-----------------------------|---------------------------------|
| Age (yr) | 46.66 \pm 10.36 | 44.6 \pm 8.17 |
| BMI (kg/m ²) | 26.34 \pm 3.91 | 27.77 \pm 2.91 |
| RBG (mmol/l) | 5.74 \pm 1.14 | 5.36 \pm 1.12 |
| pp TG (mmol/l) | 2.72 \pm 0.65 | 1.76 \pm 0.53 ^{***} |
| S. Cholesterol (mmol/l) | 5.78 \pm 0.68 | 4.27 \pm 0.70 ^{***} |
| S. HDL (mmol/l) | 0.85 \pm 0.13 | 1.18 \pm 0.22 ^{***} |
| S. LDL (mmol/l) | 3.4 \pm 0.7 | 2.96 \pm 0.57 ^{***} |
| S. VLDL (mmol/l) | 1.24 \pm 0.3 | 0.81 \pm 0.24 ^{***} |
| Ath. index | 4.17 \pm 1.26 | 2.6 \pm 0.76 ^{***} |
| B. Urea (mmol/l) | 28.58 \pm 10.94 | 5.85 \pm 0.74 ^{***} |
| S. Creatinine (μ mol/l) | 551.0 \pm 326.15 | 74.4 \pm 7.79 ^{***} |
| S. FSH (IU/l) | 10.14 \pm 4.24 | 6.32 \pm 1.47 ^{***} |
| S. LH (IU/l) | 11.78 \pm 5.23 | 5.28 \pm 2.1 ^{***} |
| S. Total Testosterone (nmol/l) | 8.81 \pm 3.43 | 15.17 \pm 5.59 ^{***} |
| S. SHBG (nmol/L) | 35.5 \pm 21.89 | 32.94 \pm 13.52 |
| S. Free Testosterone (pmol/l) | 20.63 \pm 13.89 | 32.16 \pm 13.19 |

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

Figures:

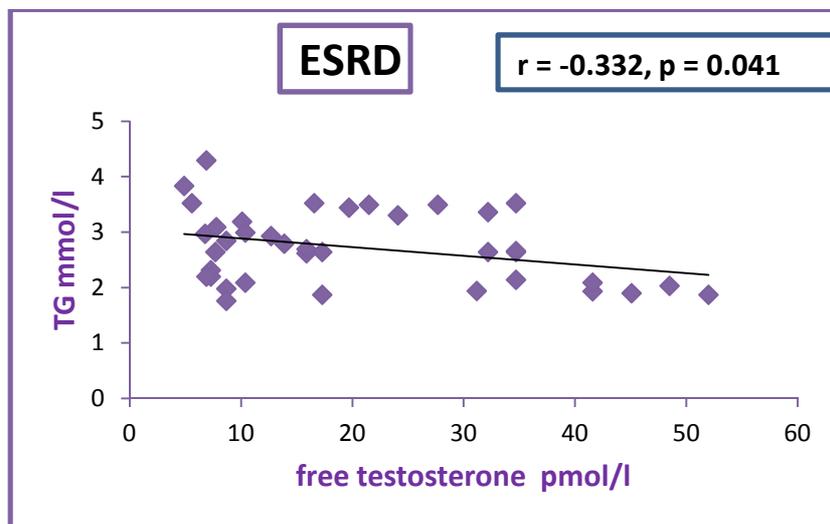


Figure (1): Correlation between total testosterone and postprandial triglyceride.

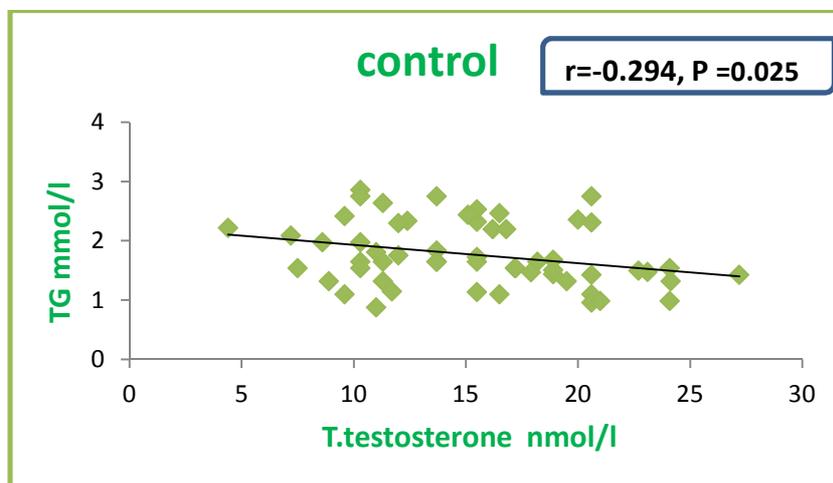


Figure 2: Correlation between free testosterone, and postprandial triglyceride.

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