TESTOSTERONE LEVELS IN NONDIALYSIS DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract
Several studies have shown that endocrine abnormalities are a common feature in patients with renal failure. The aim of this study was to examined the testosterone levels in nondialysis diabetic patients with chronic kidney disease (CKD).26 patients with type 2 diabetes (T2DM), aged between 45 and 66 years and level of glomerular filtration rate (GFR)30 ml/min/1.73m^2 were recruited for this study. Biochemical and hormonal parameters: the fastind plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), total and free testosterone were measured. FPG was determined using automatic devices, HbA_{1c} by high-performance liquid chromatography (HPLC), total testosterone by electro-chemiluminescence immunoassay (ECLIA) and free testosterone by enzyme-linked immunosorbent assay (ELISA). Low testosterone levels were confirmed by two separate blood testosterone measurements. Results were compared with the same measurements in 22 subjects with T2DM but without CKD. The groups were similar in terms of age, FPG and HbA_{1c}. Total testosterone and free testosterone are significantly low values in diabetic patients with CKD than contol group (12.97 nmol/l vs 17.89 nmol/l p=0.0096, 0.06 nmol/l vs 0.009 nmol/l, p=0.0198). Our study demonstrates that serum testosterone levels gradually decline with progressive CKD and age.
Key words*: testosterone levels, diabetes, chronic kidney disease*

INTRODUCTION

Chronic kidney disease (CKD) is associated with endocrine abnormalities such hyperprolactinaemia, increased prevalence of low T3 syndrome and subclinical hypothyroidism, secondary hyperparathyroidism, hypogonadism [1, 2, 3, 4].
Several studies suggests that testosterone deficiency is the most common gonadal alteration in men with CKD [4, 5]. Changes of testosterone synthesis and/or metabolism develop early after the onset of deterioration of kidney function. The mechanism of low testosterone levels in patients with renal insufficiency remains unclear, but several aetiologic factors appear to contribute to the described changes: primary hypogonadism, disturbances of the hypothalamic–pituitary axis, uraemic toxins, co-morbidity and concomitant drug administration [4]
A large evidence base suggests that testosterone deficiency may be a risk factor for the onset, progression of cardiovascular disease (CVD) [5, 6, 7] and low testosterone values were associated with increased risk of death in male hemodialysis patients [8, 9]. In an issue of the *Clinical Journal of the American Society of Nephrology,* published in 2011 entitled: "Endogenous Testosterone, Endothelial Dysfunction, and Cardiovascular Events in Men with Nondialysis Chronic Kidney Disease, " Yilmaz MI *et al* report that "*Total and free testosterone levels decreased in parallel with the reduction of kidney function. Finally, total and free testosterone emerged as predictors of future cardiovascular outcomes in nondialysis CKD patients*." [5]. A prospective observational study performed by Carrero JJ *et al,* analysed the relationship between testosterone concentration and subsequent mortality in a cohort of 126 men treated with hemodialysis (HD). They found that "*among men treated with HD, testosterone concentrations inversely correlate with all-cause and CVD-related mortality, as well as with markers of inflammation. Hypogonadism may be an additional treatable risk factor for patients with chronic kidney disease*" [8].
A large body of epidemiological data documents that diabetes is an independent risk factor for CVD [10, 11, 12]. A meta-analysis published in 2010 in *Lancet* that included data for 698 782 people from 102 prospective studies concluded that "*Diabetes confers about a two-fold excess risk for a wide*

range of vascular diseases, independently from other conventional risk factors"[12].
The aim of this study was to examined the testosterone levels in nondialysis diabetic patients with CKD.

MATERIAL AND METHOD

26 patients with type 2 diabetes (T2DM), aged between 45 and 66 years and level of glomerular filtration rate (GFR)>30 ml/min/1.73m^2 were recruited for this study. Biochemical and hormonal parameters: the fastind plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), total and free testosterone were measured. FPG was determined using automatic devices, HbA_{1c} by high-performance liquid chromatography (HPLC), total testosterone by electro-chemiluminescence immunoassay (ECLIA) normal range 9.9-27.8 nmol/l and free testosterone by enzyme-linked immunosorbent assay (ELISA), normal range 0.019-0.145 nmol/l. Low testosterone levels were confirmed by two separate blood testosterone measurements. Results were compared with the same measurements in 22 subjects with T2DM but without CKD.

STATISTICAL ANALYIES

Data are presented as mean±SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate correlations between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

RESULTS

The groups were similar in terms of age, FPG and HbA_{1c}. Total testosterone and free testosterone are significantly low values in diabetic patients with CKD than contol group (12.97 nmol/l *vs* 17.89 nmol/l p=0.0096, 0.06 nmol/l *vs* 0.009 nmol/l, p=0.0198).Table 1 gives characteristics of patients with T2DM and CKD and control group recruited in study.

Table 1. Characteristics of patients with T2DM and CKD and control group recruited in study,
(signifiant at the 0.05 level: p<0.05)

	Characteristics of study group (n=26)	Characteristics of control group (n=22)	P
Age (years)	**56.50±6.35**	**54.18±7.20**	**NS**
FPG (mg/dl)	**194.12±42.26**	**195.64±45.62**	**NS**
HbA_{1c} (%)	**7.94±0.74**	**7.94±0.79**	**NS**
GFR (ml/min/1.73m^2)	**67.54±18.52**	**100.18±4.90**	**<0.0001**
Total testosterone (nmol/l)	**12.97±6.31**	**17.89±6.14**	**0.0096**
Free testosterone (nmol/l)	**0.06±0.05**	**0.09±0.05**	**0.0198**

Accordind the National Kidney Federation-Kidney Dialysis Outcomes Quality Initiative (K/DOQI) 16 patients of study group (61.53%) are included in stage 2 (kidney damage with mild reduction of GFR, GFR between 60 and 89 ml/min/1.73m$^{2)}$ and 10 patients 38.40%) in stage 3 (kidney damage with moderate reduction of GFR, GFR between 30 and 59 ml/min/1.73m^2) [13].

Among the 26 T2DM patients with CKD, the prevalence of low testosterone was 50.00% (13 patients). In the control group the prevalence of low testosterone was 22.72% (5 subjects). 3 patients of study group (11.53%) and 1 patient of control group (4.54%) present testosterone levels in the lower range of normality.

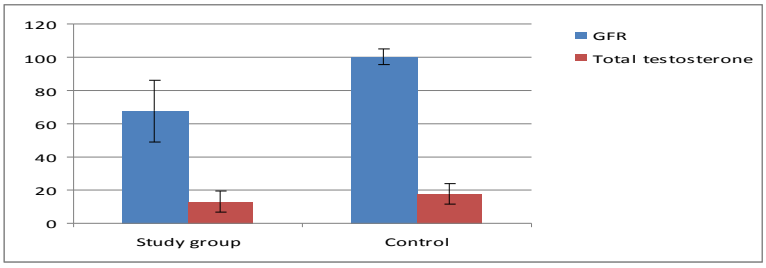

Figure 1. Levels of total testosterone in study and control group

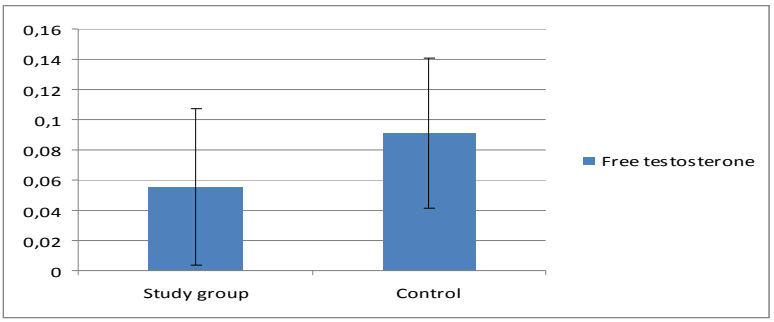

Figure 2. Levels of free testosterone in study and control group

DISSCUTIONS

In agreement with previous studies in CKD patients, 50% of our patients presented testosterone levels below the normal range, and 11.53% testosterone levels in the lower range of normality [14, 15]. A study from Albaaj F *et al* reported that "*56 (26.2%) patients had significantly low testosterone levels and another 65 (30.3%) had low normal levels*." The study included 214 male patients, 62 were receiving haemodialysis, 22 continuous ambulatory peritoneal dialysis, 34 patients had functioning renal transplants and 96 patients were in the low clearance phase [14].

Present study showed inverse association between testosterone levels and age (Figure 3) and GFR (Figure 4).

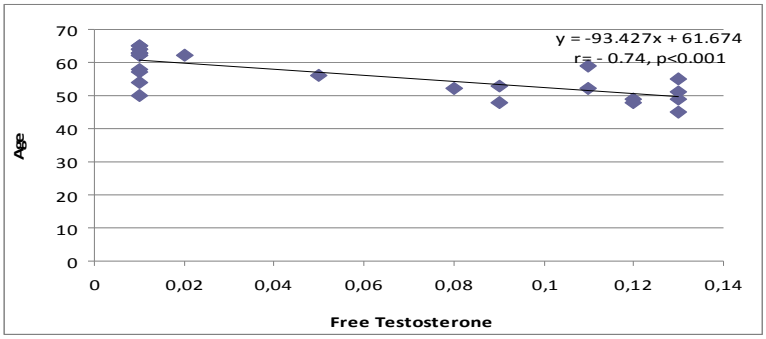

Figure 3. Correlation between testosterone levels and age

Serum testosterone levels gradually decline as men age and this age-related decline has been confirmed in several cross-sectional and longitudinal studies [16, 17, 18]. In one large cross-sectional study published in 2008 in *The Journal of Clinical Endocrinology and Metabolism,* Wu FC *el al* report that serum testosterone concentration fell 0.4% per year, free testosterone concentration 1.3% [17]. In another study published in 2001 in the same jornal, Harman SM *et al* analysed the declines in total and/or free testosterone levels with age, in men. They report that "*age-related longitudinal decreases in testosterone and free testosterone, resulting in a high frequency of hypogonadal values*" [18].

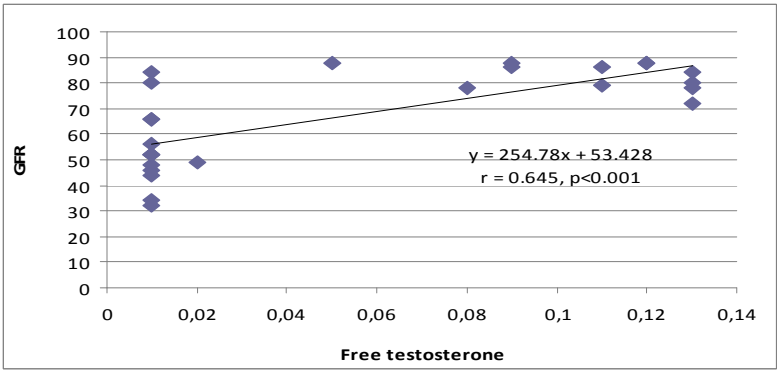

Figure 4. Correlation between testosterone levels and GFR

Serum testosterone levels gradually decline with progressive CKD. Yilmaz MI et al report that in 239 CKD male patients the overall prevalence of hypogonadism was 33% and hypogonadism increased from 17% in CKD stage 1 to 57% of the patients in CKD stage 5 [5].

CONCLUSION

Our study demonstrates that serum testosterone levels gradually decline with progressive CKD and age.

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