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Characteristics of Testosterone Deficiency Syndrome in Men With Chronic Kidney Disease and Male Renal Transplant Recipients: A Cross-Sectional Study

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ABSTRACT

Objectives. Testosterone deficiency syndrome (TDS) is common among male patients with chronic kidney disease (CKD). We compared the characteristics of TDS in men with CKD versus renal transplantation (RT) with those of age-matched normal controls.

Materials and Methods. The 129 patients were: RT recipients ($n = 25$) group I, CKD patients ($n = 37$) group II, and controls ($n = 67$). We performed estimates of testosterone, hemoglobin (Hgb), hematocrit (Hct), glucose, creatinine, and lipid profile. Self-assessment questionnaires—International Index of Erectile Function (IIEF), Aging Males' Symptoms (AMS), Center for Epidemiologic Studies Depression Scale—were used to evaluate erectile function, testosterone deficiency, and depression, respectively. We also investigated morning erection as well as the presence and duration of erectile dysfunction (ED).

Results. Group I (RT) showed significantly higher serum testosterone levels than group II (CKD), who displayed significantly worse erectile function, more severe testosterone deficiency symptoms, and a greater trend toward depression. Similarly, the prevalences of ED and TDS were significantly greater in group II than group I. Group I and controls differed significantly only in the results of serologic tests, such as serum creatinine, Hgb, and glucose and lipid profiles, but not in serum testosterone levels, scores of self-assessment questionnaires, or prevalence of ED or TDS. Serum testosterone levels correlated significantly with scores on the IIEF and AMS questionnaires in both group II and controls, but not group I.

Conclusions. RT recipients showed higher serum testosterone levels and a lower prevalence of TDS with milder symptom severity than CKD patients. RT recipients beyond the early acute posttransplant period, displayed serum testosterone levels and TDS prevalence similar to those of healthy controls. Unlike CKD patients and normal controls, serum testosterone did not significantly influence TDS symptoms in RT recipients.

ERECTILE DYSFUNCTION (ED) is commonly observed in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1] The prevalence of ED among CKD men is estimated to be about 50%.[2] Multiple hormonal abnormalities have been discovered to be among the underlying causes of ED in CKD.[3–5] Testosterone deficiency (TD), is the most common hormonal alteration, is due to reduced prolactin clearance[6] and uremic inhibition of the luteinizing hormone effect on Leydig cells.[7] According to recommendations, the clinical and biochemical alterations associated with this condition in CKD men can be diagnosed as TD syndrome (TDS). It markedly lowers the quality of life and decreases the functions of multiple organ systems.[8] Hence, one main

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concern is the impact of renal transplantation on TDS in CKD patients. Several studies have imported that most endocrine abnormalities are reversed after successful renal transplant (RT) with improved erectile function. However, the pattern of changes in testosterone levels varies according to the time after transplantation.[9,10] Furthermore, the majority of studies have not considered the changes in the prevalence and severity of ED or TDS after RT or the correlation between testosterone levels and the severity of those symptoms. Additionally, there is little information about the extent of recovery of clinical and biochemical values after RT relative to the normal range. Therefore, we investigated the characteristics of TDS among male CKD subjects and RT recipients compared with age-matched, normal controls.

MATERIAL AND METHODS

From December 2011 to June 2012, we consecutively included 129 male RT recipients ($n = 25$; group I) CKD, stage II to V, ($n = 37$ group II), and age-matched normal controls from our health promotion center ($n = 67$; control group). After obtaining consent for the study, each patient was interviewed by the same physician with regard to their past medical history, including comorbidities, onset and cause of CKD, duration of maintenance hemodialysis, time of RT, erectile function, including its presence and duration of ED as well as morning erection. Group I was questioned about ED before RT, improvement after RT and present ED. Three self-assessment questionnaires—the International Index of Erectile Function (IIEF), the Aging Males' Symptoms (AMS), and the Center for Epidemiologic Studies Depression Scale (CES-D)—were administered to evaluate the severity of ED, TD symptoms, and depression, respectively. After completing the personal interview and the self-assessment questionnaires, we performed measurements of plasma testosterone, hemoglobin (Hgb), hematocrit (Hct), creatinine, and glucose and lipid profile between 9 and 11 AM. Testosterone deficiency was defined as a plasma testosterone level <350 ng/dL. Statistical analysis employed the independent samples students *t*-test, chi-square test, simple correlation test, and multiple regression analysis. A P value <.05 was considered significant.

RESULTS

There was no difference in age among the three groups; group I, 53.5; group II, 55.0; and controls, 52.16. The present comorbidities and causes of CKD did not differ significantly between groups I and II. The mean time from the first diagnosis of CKD was significantly by different; group I, 190 months (range, 12–480) versus group II, 108 months (range, 5–280; $P = .023$). In addition, the duration of maintenance hemodialysis in group I (mean, 22.0 months; range, 3–78) was significantly shorter than that of group II (mean, 53.4 months; range, 3–156; $P = .008$). The mean time since RT in group I, was 124 months (range, 11–288). Among the 25 RT recipients, 21 (84%) experienced ED before RT and 19 of the 21 (90.5%) reported improved function after RT.

Among the 37 group II patients, 18 had ESRD; those with and without ESRD differed significantly in the severity of ED and TDS, according to their total scores of IIEF and AMS ($P = .004$ and $P = .000$, respectively). Similarly, the CES-D score of men with ESRD was higher than that of patients with stage II to IV CKD ($P = .103$). With respect to plasma testosterone levels, subjects with ESRD displayed lower levels of testosterone than those without ESRD: mean testosterone, 264.2 versus 371.6 ng/dL, ($P = .070$). Among group II patients, the prevalence of ED and TDS differed significantly between patients with ESRD versus those with less severe CKD ($P = .021$ and $P = .004$, respectively). Likewise, morning erection was reported less frequently (5.6%) by ESRD patients than by those with less severe CKD (21.1%; $P = .168$; Table 1).

Comparison between group I and group II revealed the former cohort to display significantly higher serum testosterone than group II: mean, 515.7 versus 323.5 mg/dL ($P = .001$). With respect to the scores of the IIEF, AMS, and CES-D, group Il showed significantly worse erectile function, more severe TD symptoms, and greater tendencies toward depression than group I. Similarly, the prevalences of ED and TDS were significantly higher in group II than group I ($P = .008$ and $P = .019$); (Table 2).

Comparison of group I with the 18 group II patients with stages II to IV CKD revealed a similar pattern of significant differences. RT recipients displayed higher testosterone levels, more tolerable symptom scores on (IIEF, AMS, and CES-D), and lower prevalences of ED and TDS than patients with stages II to IV CKD.

RT recipients (group 1) were compared with normal controls. Although significant differences were noted in the results of serum creatinine, Hgb, Hct, glucose, and lipid profiles, there was no difference in serum testosterone levels (493.9 vs 515.7 ng/dL; $P = .658$). The total scores on self-assessment questionnaires (IIEF, AMS, and CES-D) also did not differ significantly between these two groups ($P = .354$, .684, and .256 respectively). The prevalences of ED and TDS among group I were not significantly different from those of the controls ($P = .382$ and .390, respectively; Table 2).

The correlation between serum testosterone levels and symptom severity was investigated using simple correlation tests. Both group II and controls displayed significant correlations of serum testosterone levels with IIEF and AMS scores ($P < .05$). However there were no correlations in group I between serum testosterone levels and self-assessment questionnaire scores ($P > .05$). Multiple regression analysis to assess the impact of plasma testosterone levels on symptom severity among the multiple variables of plasma Hgb, Hct, creatinine, and glucose and lipid profile revealed a similar pattern of significance between plasma testosterone levels and self-assessment questionnaires scores in both group II and controls ($P < .05$). However, plasma testosterone levels did not show a significant impact on symptom severity in group I ($P > .05$).

DISCUSSION

The incidence of testosterone deficiency varies from 6% to 9.5% in the community and increases to 15% to 30% among

Table 1. Differences Between Patients With and Without End-Stage Renal Disease in Group II

	ESRD ($n = 18$)	CKD Stage II–IV ($n = 19$)	*P*
Hemoglobin (g/dL)	10.71 (9.96–11.46)	10.88 (9.54–12.2)	.822
Hematocrit (%)	32.43 (30.06–34.81)	32.01 (28.14–35.88)	.848
Creatinine (mg/dL)	8.94 (7.36–10.53)	3.96 (2.28–5.64)	.000
Fasting blood sugar (mg/dL)	169.2 (136.9–201.5)	120.2 (102.0–138.4)	.008
Cholesterol (mg/dL)	119.4 (103.2–135.7)	143.9 (126.2–161.6)	.040
Triglyceride (mg/dL)	126.5 (88.6–164.4)	132.6 (96.1–169.0)	.809
High-density lipoprotein (mg/dL)	39.3 (30.0–48.6)	39.8 (34.5–45.2)	.911
Low-density lipoprotein (mg/dL)	94.7 (79.7–109.6)	103.9 (88.5–119.4)	.371
Testosterone (ng/dL)	264.2 (199.0–329.4)	371.6 (271.6–471.7)	.070*
IIEF (EF)	3.22 (1.12–5.32)	9.95 (5.59–14.3)	.007
IIEF (OF)	1.17 (0.44–1.90)	4.47 (2.45–6.50)	.003
IIEF (SD)	3.33 (2.40–4.27)	5.68 (4.29–7.08)	.006
IIEF (IS)	1.11 (0.12–2.10)	3.79 (1.70–5.88)	.022
IIEF (OS)	2.78 (2.34–3.21)	4.47 (3.34–5.60)	.007
IIEF (total)	11.6 (7.66–15.6)	25.9 (17.1–34.6)	.004
AMS (sexual)	19.4 (17:8–21.0)	11.8 (8.92–14.8)	.000
AMS (somatic)	21.3 (18.5–24.2)	15.2 (12.2–18.2)	.003
AMS (psycho)	12.6 (10.6–14.5)	9.05 (6.27–11.8)	.038
AMS (total)	53.1 (48.8–57.5)	36.1 (28.3–43.9)	.000
CES-D	25.9 (22.0–29.8)	19.6 (13.0–26.3)	.103
ED prevalence (%)	94.4	63.2	.021
TDS prevalence (%)	94.4	52.6	.004
Morning erection (%)	5.56	21.1	.168

Abbreviations: AMS, Aging Males' Symptoms; CES-D, Center for Epidemiologic Studies Depression Scale; ED, erectile dysfunction; IIEF, International Index of Erectile Function; TDS, testosterone deficiency syndrome.
*Marginal statistical significance.

men with diabetes or obesity.[11,12] Among patients with ESRD, definite TD occurs among about 44%, testosterone insufficiency, about 33%, and normal testosterone levels, only 23%, according to the Carerro et al.[13] In contrast, nearly 95% of ESRD patients showed TDS in the present study. We believe that the much higher rate of TDS observed in this study was caused by the more severe spectrum of ESRD patients in this study; all of ESRD patients had undergone maintenance hemodialysis for average 53.4 months (range, 3–156). The pathophysiologic causes for the high prevalence of TDS among CKD patients, although not completely determined, include hypothalamic–pituitary–testicular axis dysfunction, as well as decreased synthesis and secretion of testosterone during progression of CKD.[6,7,14] In the present study, lower testosterone levels and worse TDS symptom were also associated with the stage of CKD. The ESRD group displayed significantly lower testosterone levels and more severe TDS symptoms than did patients with earlier stages of CKD. In addition, it is known that endocrinologic deterioration in CKD is the main reason for sexual dysfunction; these abnormalities may persist despite dialysis therapy.[15–17] Consistent with these patterns, the present study noted significant correlations between serum testosterone levels and the severities of ED and TDS in CKD patients. Several studies have reported correction of uremia by RT restores the pituitary-gonadal axis.[18–20] The increased mean testosterone with suppressed luteinizing hormone and restored serum prolactin levels indicate Leydig cell function recovery after transplantation.[1] However, the recovery of gonadotropic hormones is variable; it is known to be affected by both the time after transplantation and the doses of immunosuppressants.[10] Shamsa et al[9] reported that the levels of testosterone at 4 weeks after RT were lower than those before RT. According to Saha et al,[10] immunosuppressants, especially high-dose corticosteroids, cause persistent malfunction of the pituitary-gonadal axis during the first weeks after RT. The 31.8% prevalence of TDS in RT recipients in the present study was similar to that of controls and significantly lower than that among the CKD groups. However, high-dose immunosuppressants no longer affected RT recipients in this study, because the mean time after RT was 124 months. A period of at least 1 year may be necessary for significant hormonal changes; a similar time after renal transplantation seems to be required for uremic men to increased testosterone levels.[21,22] With respect to TDS in RT recipients, erectile dysfunction is the key component; the prevalence of TDS showed a tendency similar to that of ED. Several studies about the effect of RT on erectile function had conflicting results.[9,23,24] Some workers have reported renal transplantation to improve erectile function with normalized endocrine factors.[9,24]; others have failed to note significant improvement in erectile function after renal transplantation.[23] The conflicting results were probably caused by the multifactorial pathophysiology of ED and methodologic differences. Some studies were performed relatively soon after renal transplantation, others assessed erectile function using self-assessment questionnaires at diverse time points

Table 2. Comparison of the three groups' serological values, self-assessment questionnaires and prevalence of ED and TDS (Mean (95% confidence interval) or percentage)

	Controls ($n = 67$)	Group I ($n = 25$)	Group II ($n = 37$)	P^*
Age (y)	52.2 (49.6–54.7)	53.5 (48.4–58.6)	55.0 (49.5–60.5)	.694
Hemoglobin (g/dL)	15.2 (15.0–15.5)	13.7 (12.8–14.7)	10.8 (9.89–11.7)	.000
Hematocrit (%)	44.7 (43.9–45.4)†	41.0 (38.3–43.6)	31.9 (29.3–34.5)	.000
Creatinine (mg/dL)	0.88 (0.85–0.91)†	1.22 (1.05–1.38)	6.07 (4.39–7.75)	.000
Fasting blood sugar (mg/dL)	95.6 (90.6–100.6)†	112.9 (106.4–119.4)	141.3 (118.6–163.9)	.037
Cholesterol (mg/dL)	182.6 (174.6–190.7)†	167.6 (158.5–176.8)	132.7 (118.4–147.0)	.000
Triglycerides (mg/dL)	149.0 (128.6–169.5)	135.4 (111.3–159.4)	141.2 (112.4–170.0)	.764
High-density lipoproteins (mg/dL)	50.8 (48.1–53.4)†	58.4 (51.1–65.7)	36.8 (32.4–41.1)	.000
Low-density lipoproteins (mg/dL)	120.8 (112.2–129.5)†	100.8 (91.9–109.7)	98.3 (86.1–110.5)	.750
Testosterone (ng/dL)	493.9 (447.9–539.9)	515.7 (415.4–616.0)	323.5 (256.2–390.8)	.001
IIEF (EF)	18.5 (16.2–20.8)	18.0 (14.5–21.6)	7.90 (4.84–11.0)	.000
IIEF (OF)	6.93 (5.98–7.89)	7.32 (5.85–8.78)	3.37 (1.96–4.77)	.000
IIEF (SD)	6.67 (6.18–7.15)	6.64 (5.89–7.38)	4.93 (3.87–5.99)	.015
IIEF (IS)	9.68 (8.27–11.09)	7.64 (5.55–9.72)	2.93 (1.49–4.38)	.000
IIEF (OS)	6.50 (5.92–7.08)	6.00 (5.17–6.83)	3.80 (3.01–4.59)	.000
IIEF (total)	45.8 (40.5–51.1)	45.6 (38.1–53.1)	21.4 (15.2–27.6)	.000
AMS (sexual)	9.08 (8.15–10.02)	9.77 (7.99–11.55)	14.5 (12.1–16.8)	.003
AMS (somatic)	12.1 (11.1–13.0)	12.1 (10.5–13.6)	16.8 (14.6–19.0)	.002
AMS (psycho)	7.05 (6.41–7.69)	7.32 (5.99–8.65)	10.4 (8.32–12.5)	.023
AMS (total)	28.4 (26.0–30.7)	28.7 (24.6–32.6)	41.6 (35.8–47.5)	.001
CES-D	8.02 (6.04–10.0)	10.3 (6.42–14.1)	22.1 (17.3–26.8)	.103
ED prevalence (%)	26.5	36.3	73.3	.008
TDS prevalence (%)	23.9	31.8	66.7	.019
Morning erection (%)	73.2	68.2	16.7	.000

Abbreviations as in Table1.
*Comparison between groups I and II.
†Significant difference between group I and controls.

after RT. Meanwhile, this study was a cross-sectional study, conducted relatively long after renal transplantation. Consequently, in this study, 90.5% of RT recipients who had ED before RT experienced improvement of erectile function after RT and the prevalence of ED of RT recipients was significantly lower than that of the patients with CKD. In the present study, in each group, the correlation between serum testosterone and symptom severity was investigated to understand better the relationship between testosterone and sexual function. According to Basar et al,[25] serum free testosterone levels significantly correlated with IIEF scores and total and free testosterone levels correlated with the score of andrologic symptoms reported on the AMS. In this study, we noted significant correlations between serum testosterone levels and IIEF and AMS scores, both in the controls and CKD patients. However, there were no correlations within RT recipients indicating no influence of serum testosterone on TDS symptoms in RT recipients.

There were several limitations in the present study. First, the size of the CKD and RT groups was relatively small, rendering statistical power to be limited. Second, because the investigation was designed as a cross-sectional study, only the present clinical characteristics were measured; we could not thoroughly analyze the time course of changes in TDS. Finally, because our analysis of symptom severity of ED and TDS relied on self-assessment questionnaires, biased reporting is a concern. The subject's attitudes, psychological status, and confidence in their health differed for each group. These differences may have influenced these self-assessments.

Notwithstanding these limitations, our approach had strengths relative to previous studies, which focused on changes in testosterone levels and erectile function after RT. Notably, we evaluated the clinical significance of the testosterone levels and erectile function after RT by comparing them with normal controls. In the present study, testosterone levels, and symptom severity, as well as ED and TDS prevalences did not differ from those of the age-matched normal controls. Although it was a cross-sectional study, we noted a significant role of RT to improve TDS symptoms among CKD patients.

In conclusion, RT recipients displayed higher serum testosterone levels and a lower prevalence of TDS with milder symptom severity than chronic kidney disease patients. Renal recipients beyond the acute posttransplant period revealed serum testosterone levels and TDS prevalence similar to those of healthy controls. Unlike CKD patients and normal controls, serum testosterone did not significantly influence TDS symptoms in RT recipients.

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