Endogenous Testosterone and Mortality in Male Hemodialysis Patients: Is It the Result of Aging?

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Background and objectives: Low serum testosterone levels in hemodialysis (HD) patients have recently been associated with cardiovascular risk factors and increased mortality. To confirm this observation, we investigated the predictive role of serum total testosterone levels on mortality in a large group of male HD patients from Turkey.

Design, settings, participants, & measurements: A total of 420 prevalent male HD patients were sampled in March 2005 and followed up for all-cause mortality. Serum total testosterone levels were measured by ELISA at baseline and studied in relation to mortality and cardiovascular risk profile.

Results: Mean testosterone level was 8.69 ± 4.10 (0.17 to 27.40) nmol/L. A large proportion of patients (66%) had testosterone deficiency (<10 nmol/L). In univariate analysis, serum testosterone levels were positively correlated with creatinine and inversely correlated with age, body mass index, and lipid parameters. During an average follow-up of 32 months, 104 (24.8%) patients died. The overall survival rate was significantly lower in patients within the low testosterone tertile (<6.8 nmol/L) compared with those within the high tertile (>10.1 nmol/L; 64 *versus* 81%; $P = 0.004$). A 1-nmol/L increase in serum testosterone level was associated with a 7% decrease in overall mortality (hazard ratio 0.93; 95% confidence interval 0.89 to 0.98; $P = 0.01$); however, this association was dependent on age and other risk factors in adjusted Cox regression analyses.

Conclusions: Testosterone deficiency is common in male HD patients. Although testosterone levels, *per se*, predicted mortality in this population, this association was largely dependent on age.

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Low serum testosterone levels have been associated with several components of metabolic syndrome, including cardiovascular disease (CVD), hypertension, abdominal obesity, insulin resistance, and inflammatory markers in male individuals without uremia, independent of age decline (1,2). Also, it has been shown that low endogenous testosterone levels are associated with increased risk for both all-cause and cardiovascular mortality (3–12). Evidence from short-term studies indicated that testosterone replacement therapy may improve some specific cardiovascular risk factors, such as visceral obesity, insulin resistance, lipid and inflammatory profiles, and exercise-induced cardiac ischemia (13).

Testosterone deficiency is a common finding in hemodialysis (HD) patients, most probably as a result of altered sex-hormone metabolism (14); however, the prevalence of male hypogonadism and the involvement of testosterone deficiency in the risk profile of HD patients are not well explored. In a small study that included male HD patients without diabetes, low testosterone levels were associated with endothelial dysfunction and atherosclerosis (15). Interestingly, Carrero *et al.* (16) recently demonstrated in a Swedish HD cohort that low serum testosterone levels were significant predictors of mortality, irrespective of age and inflammation, but this was abolished after correction for serum creatinine, used there as a surrogate of muscle mass (16). In light of the exceedingly elevated (cardiovascular) mortality of HD patients (17), this possibility is an attractive and therapeutically modifiable idea. We aimed in this study to investigate the prevalence of testosterone deficiency as well as its impact on overall outcome in a large prospective cohort of prevalent male Turkish patients who were undergoing HD.

Materials and Methods

Patients

In March 2005, 773 patients (445 male) who were on thrice-weekly conventional HD were recruited for a cross-sectional observational study with mortality follow-up from 10 dialysis centers operated by Fresenius Medical Care in Turkey. The only inclusion criteria were to be aged older than 18 years and having a serum sample collected at the time of enrollment (March 2005). This study focused on the 445 available men. Exclusion criteria were presence of serious comorbid situations that would lead to a poor 1-year life expectancy, namely active malignancy, active infection, congestive heart failure (New York Heart

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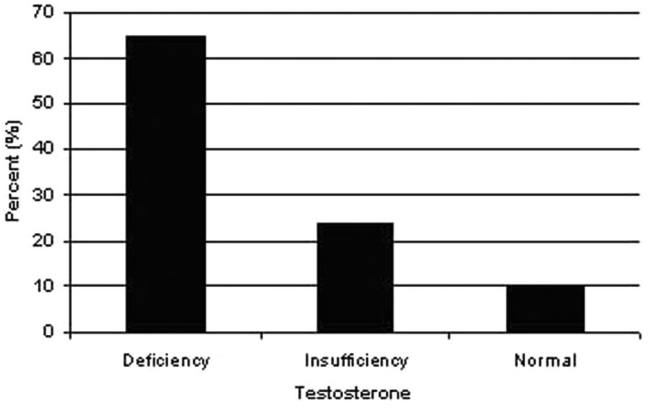

Figure 1. Prevalence of normal testosterone levels (>14 nmol/L), insufficiency (10 to 14 nmol/L), and deficiency (<10 nmol/L) in the study population.

Association classes 3 to 4, mainly as a result of ischemic heart disease), chronic obstructive pulmonary disease with respiratory failure or right-sided heart failure (stages 3 to 4), or advanced hepatic cirrhosis (Child-Plough stage C). Twenty-five men were excluded according to these criteria, and the final analysis included 420 men. No patients received sex hormones, sex hormone antagonists, or anabolic steroids. The study was approved by the local ethics committee, and informed consent was obtained from all patients. The study was performed according to the recommendations of the Declaration of Helsinki.

One hundred male patients (24%) had diabetes, and 147 (35%) had a history of CVD. Five percent of the patients were on angiotensin-converting enzyme inhibitors, 7% were on β blockers, and 5% were on calcium channel blockers. Antihyperlipidemic and erythropoiesis-stimulating agents were used by 5.8 and 37.4%, respectively. Forty-four percent of the patients were undergoing dialysis in the morning session and the rest in the afternoon. Demographic characteristics, medical history, and biochemical parameters were collected from patients' history forms at baseline. Follow-up data of the patients including date of death were prospectively collected in HD centers as reported by the European Clinical Dialysis Database (EuCliD) in Turkey. Overall mortality was assessed for up to 48 months of follow-up.

Laboratory Measurements

Blood samples were collected at the beginning of the HD session at baseline. Serum samples were separated and kept frozen at −70°C. Serum total testosterone levels were measured by ELISA (AxSYM; Abbott Diagnostic). All biochemical parameters including albumin, hemoglobin, calcium, phosphate, creatinine, and high-sensitivity C-reactive protein (hs-CRP) were performed by standard autoanalyzers (Architect C8000 and CELL-DYN 3700; Abbott) in the same central laboratory registered to external quality-controlled programs. Normal testosterone level was defined as testosterone >14 nmol/L, low-normal as between 10 and 14 nmol/L, and low as <10 nmol/L.

Statistical Analysis

All parameters were expressed as mean ± SD. $P < 0.05$ was considered statistically significant. Comparisons between two groups were assessed with unpaired *t* test or Mann-Whitney *U* test, as appropriate. Differences between more than two groups were analyzed by ANOVA. Pearson and Spearman rank correlations were used to assess correlations of testosterone with other variables. Multiple linear logistic analysis was used to determine predictors of testosterone level. For these analyses, missing values for biochemical parameters other than testosterone were computed with the average value of the group. Overall survival rates were analyzed by Kaplan-Meier survival curve; Cox proportional hazard model was used to identify independent predictors of survival. The predictive role for all-cause mortality of serum testosterone levels as a continuous variable was investigated in crude and adjusted models using the Cox regression analysis and adjusting for age, diabetes, CVD history, HD duration, body mass index (BMI), albumin, creatinine, and CRP levels. Patients were censored at the time of premature termination (renal transplantation, transfer to another dialysis center, or death). Because of loss of an elevated number of patients to follow-up, analyses were run as a sensitivity analysis, excluding patients who did not complete the follow-up period. All statistical analyses were performed using SPSS 15 (SPSS, Chicago, IL).

Results

Baseline Characteristics

Mean age was 54 ± 13 years, and time on HD was 54 ± 49 months. Mean value of serum total testosterone was 8.69 ± 4.10 (0.17 to 27.40) nmol/L. A total of 277 (66%) patients had testosterone deficiency on the basis of their biochemical assessment (testosterone <10 nmol/L), 101 (24%) patients had testosterone levels in the lower range of normality (10 to 14 nmol/L), and 42 (10%) patients were considered to have normal testosterone values (>14 nmol/L; Figure 1). Patients samples were taken before the HD session in the morning or afternoon rounds. A brief comparison showed no difference between the patients who were treated in morning and in afternoon HD sessions with regard to testosterone levels, age, time on HD, presence of diabetes, and CVD history (Table 1).

Table 2 shows the clinical and laboratory characteristics of the patients according the testosterone tertiles. The patients with low testosterone level displayed older age and higher prevalence of CVD. In addition, BMI, serum calcium, and lipid parameters were higher, whereas serum albumin and creati-

Table 1. Comparison of patients included in the study according to morning or afternoon sampling

Parameter	Morning Sampling (n = 185)	Afternoon Sampling (n = 235)	P
Age (years; mean ± SD)	54.4 ± 13.7	52.4 ± 15.7	0.2
Dialysis vintage (months; mean ± SD)	54.6 ± 46.3	47.2 ± 45.2	0.2
CVD history (%)	18	15	0.5
Diabetes (%)	22	24	0.6
Testosterone (nmol/L; mean ± SD)	9.20 ± 4.52	8.44 ± 3.87	0.1
hs-CRP (mg/dl; mean ± SD)	1.55 ± 2.08	1.88 ± 2.39	0.2

Table 2. Demographic, clinical, and laboratory data of the testosterone tertiles

Parameter	Lower Tertile (<6.8 nmol/L)	Middle Tertile (6.8 to 10.1 nmol/L)	Higher Tertile (>10.1 nmol/L)	*P*	Rho (*P*)
n	140	141	139		
Testosterone (nmol/L; mean ± SD)	4.57 ± 1.8	8.2 ± 0.9	13.2 ± 3.0	—	—
Age (years; mean ± SD)	58 ± 14	52 ± 14	50 ± 15	<0.001	−0.21 (<0.001)
Dialysis vintage (months; mean ± SD)	48 ± 50	55 ± 51	59 ± 48	0.16	0.13 (0.006)
Diabetes (%)	26	27	18	0.16	−0.07 (0.14)
CVD history (%)	23	17	12	0.04	−0.12 (0.01)
BMI (kg/m^2; mean ± SD)	24.0 ± 4.2	23.0 ± 3.7	22.3 ± 3.7	0.02	−0.19 (<0.0001)
Creatinine (mg/dl; mean ± SD)	8.6 ± 2.5	9.2 ± 2.3	9.3 ± 2.0	0.05	0.13 (0.01)
Albumin (g/dl; mean ± SD)	3.87 ± 0.42	3.99 ± 0.32	3.94 ± 0.29	0.02	0.08 (0.09)
hs-CRP (mg/dl; mean ± SD)	1.85 ± 2.10	1.57 ± 1.74	1.76 ± 2.63	0.57	−0.11 (0.04)
Calcium (mg/dl; mean ± SD)	8.8 ± 0.8	8.7 ± 0.7	8.6 ± 0.5	0.04	−0.11 (0.02)
Phosphate (mg/dl; mean ± SD)	4.9 ± 1.5	5.0 ± 1.3	5.0 ± 1.2	0.61	0.06 (0.22)
PTH (pg/ml; mean ± SD)	413 ± 452	465 ± 383	495 ± 405	0.32	0.18 (0.001)
Cholesterol (mg/dl; mean ± SD)	172 ± 46	166 ± 46	149 ± 32	<0.001	−0.22 (0.0004)
Triglyceride (mg/dl; mean ± SD)	179 ± 94	171 ± 110	131 ± 74	<0.001	−0.21 (<0.0001)
Hemoglobin (g/dl; mean ± SD)	11.5 ± 1.5	11.3 ± 1.3	11.2 ± 1.4	0.16	−0.08 (0.08)
ESA (%)	34	40	37	0.51	—

ESA, erythropoiesis-stimulating agent; PTH, parathyroid hormone.

nine levels were lower. There were no significant differences regarding HD duration, hs-CRP, hemoglobin, phosphate, and parathyroid hormone levels.

Predictors for Testosterone Levels

Univariate associations with testosterone values are presented in Table 2. Serum testosterone level was significantly correlated with age (Figure 2). In addition, testosterone levels were positively correlated with time on HD, serum creatinine, and parathyroid hormone and inversely correlated with the presence of CVD; BMI; and, total cholesterol, triglyceride, hs-CRP, and calcium levels. In multiple linear regression analysis, serum albumin levels were positively associated with testosterone levels. Also, age, BMI, and serum triglyceride and calcium levels were negative predictors of testosterone levels (Table 3).

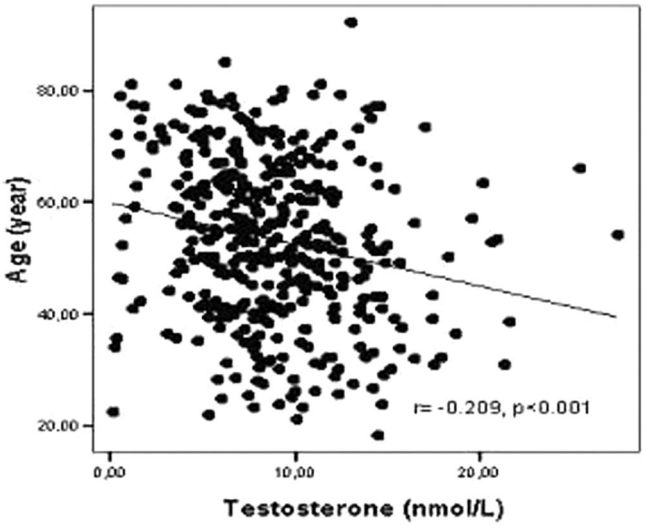

Figure 2. Univariate correlation between age and testosterone levels.

Implications on Outcome

During a mean of 32 ± 16 months of follow-up, 104 (24.8%) patients died. In addition, 87 (20%) patients were transferred to another dialysis center, and 15 (3.5%) received a transplant. The patients who died had significantly lower serum testosterone levels compared with those who survived (7.7 ± 3.5 *versus* 9.0 ± 4.2 nmol/L; $P = 0.005$). The survival rate was significantly lower for patients in the low testosterone tertile (<6.8 nmol/L) compared with those in the high tertile (>10.1 nmol/L; 64 *versus* 81%; $P = 0.004$), which was also shown in Kaplan-Meier analysis (Figure 3).

An increased risk for overall mortality for patients with low serum testosterone was found in crude Cox regression analysis (Table 4). A 1-nmol/L increase in serum testosterone level was associated with a 7% decrease in overall mortality, but this

Table 3. Stepwise multivariate regression analysis for predictors of serum testosterone level

Parameter	Estimate	SE	*P*
Intercept			<0.0001
Age (years)	−0.048	0.014	0.001
Albumin (g/dl)	1.64	0.659	0.01
Calcium (mg/dl)	−0.807	0.303	0.008
BMI (kg/m^2)	−0.108	0.053	0.04
Triglyceride (mg/dl)	−0.009	0.002	0.01

The adjusted R^2 of the model is 0.16.

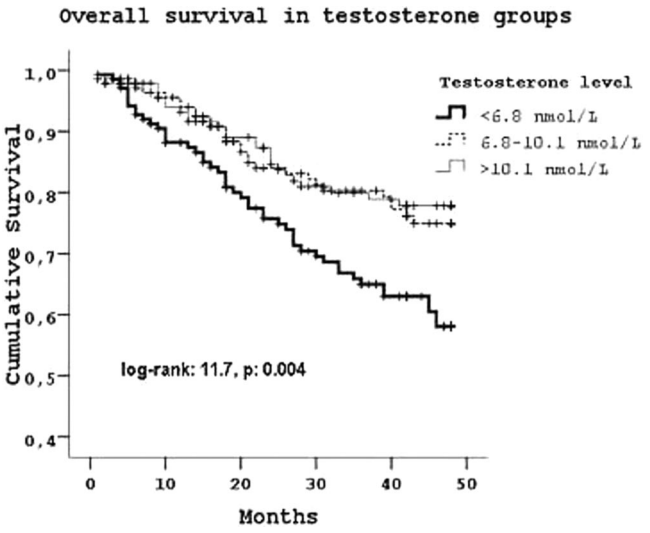

Figure 3. Cumulative survival analysis according to testosterone tertiles.

association was not independent of age or of additional risk factors (diabetes; CVD history; HD duration; BMI; and albumin, creatinine, and hs-CRP levels). The patients in lowest tertile also showed worse outcome in crude Cox analysis; however, it was again lost after adjustment for age and other confounders. We should perhaps mention that the magnitude of the hazards for the low testosterone tertile was somewhat high in fully adjusted models (HR 1.49; 95% CI 0.83 to 2.66). Additional analyses that excluded patients who did not complete the follow-up period yielded similar results (data not shown). Only age and the presence of CVD history were found to be independent predictors of mortality in fully adjusted models.

Discussion

This study identifies testosterone deficiency as a very common endocrine abnormality (65%) of Turkish male HD patients. Low testosterone is associated with poor nutritional status and increased inflammation. Although low testosterone was, in crude analysis, a significant predictor of overall mortality, this association was largely dependent on age. At first, our study reveals, in accordance with less powered and more heterogeneous populations (18,19), that testosterone deficiency is a common endocrine dysfunction in Turkish men who are treated with conventional HD. This prevalence is much increased as compared with the occurrence of testosterone deficiency in community-dwelling men aged 40 to 75 years, which is estimated to vary from 6.0 to 9.5%, rising to 15 to 30% in men with diabetes or obesity (20,21). The reasons for these endocrine alterations are not completely understood, but it seems that both testosterone synthesis and secretion decrease as renal function declines, to a large extent as a result of prolactin retention (22). In patients with uremia, both serum total and free testosterone concentrations are reduced, although binding capacity and concentration of sex hormone–binding globulin (SHBG) are normal, suggesting impairment of gonadal steroidogenesis (23,24).

Recently, Carrero *et al.* (16) identified low testosterone levels (lower tertile of distribution in that study) as an independent risk factor for all-cause and CVD mortality in a cohort of 126 prevalent HD Swedish men. In that study, the association with mortality was independent of age, SHBG, inflammation and several comorbidities but dependent of serum creatinine, suggesting a relation with muscle depletion. Our analysis, however, cannot confirm such findings, and we show that in our population, although such association with mortality exists, it is largely dependent on age. The relation of testosterone to age is parabolic, and there is a steady decline in testosterone levels with increasing age after puberty. Indeed, in the Massachusetts Male Aging Study, total testosterone levels were estimated to decline at 0.8% per year in a cross-sectional analysis, whereas a longitudinal analysis showed 1.6% per year and 2.0 to 3.0% per year declines, respectively (25).

For correct contextualization, a number of differences between our study and that of Carrero *et al.* (16) should be mentioned because they make results not fully comparable. At first, both cohorts present large differences in age, baseline comorbid conditions, and mortality rates. Surprisingly, despite that our patients were younger, the proportion of testosterone-deficient patients was larger than in Swedish patients, 52% of

Table 4. Predictors of mortality in Cox regression analysis

Parameter	Crude	Age Adjusted	Fully Adjusted[a]
Model 1: Testosterone levels			
per 1 nmol/L (HR [95% CI])	0.93 (0.89 to 0.98)	0.97 (0.92 to 1.02)	0.96 (0.89 to 1.02)
P	0.01	0.30	0.23
Model 2: Testosterone tertiles			
middle			
HR (95% CI)	1.02 (0.58 to 1.80)	1.11 (0.65 to 1.90)	0.76 (0.38 to 1.54)
P	0.9	0.68	0.46
lower			
HR (95% CI)	2.04 (1.24 to 3.35)	1.44 (0.89 to 2.32)	1.49 (0.83 to 2.66)
P	0.005	0.13	0.17

[a]Adjusted for age, HD duration, diabetes, CVD, BMI, albumin, creatinine, and CRP.

whom were found to have hypogonadism (16). We do not have a clear explanation for this, but we could speculate that our larger sample size may give a more representative estimation. Alternatively, because genetic variation in the androgen metabolic network is very large and affects testosterone action, availability, and disposition, we cannot exclude the existence of genetic differences between Swedish and Turkish patients that could have influenced our results (26). Also, vintage is much longer in our cohort, which could represent a survivor bias, because those at risk for dying would have done it earlier upon dialysis initiation. In this sense, we observed a positive association between testosterone levels and dialysis vintage in our study, although this variable was stepwise excluded in multivariate analysis. In the study of Carrero *et al.* (16), univariate associations of testosterone levels with dialysis vintage were not reported, but patients within the lower testosterone tertile tended to have increased dialysis vintage, albeit nonsignificant, which suggests an opposed association than that observed in our material. This finding may indeed indirectly support the idea that individuals with increased testosterone levels could have survived longer, although we should bear in mind that these individuals were likely to be younger as well. In sum, we should emphasize the cross-sectional nature of both studies, which allows us to report associations but not to infer causation. A second remark should be made regarding the quality of our follow-up data. Whereas the Swedish study (16) had no loss to follow-up and did not censor for transplantation, 20% of our patients moved to other clinics and 3.5% received a transplant. In addition, the inaccuracy of our death records prevents us from separating causes of death. Because Carrero *et al.* (16) reported a predictive impact of low testosterone in CVD mortality, we cannot exclude the possibility that this may have occurred in our patients also; thus, we may infer in selection bias despite that our sensitivity analysis excluded patients who were lost to follow-up produced similar results. Third, it has been demonstrated that testosterone levels have some circadian variation, being approximately 30% higher when measured in the morning as compared with the afternoon (27). Whereas the Swedish report (16) sampled in the morning, we included patients from morning and afternoon HD sessions; however, no apparent differences were observed between these two groups regarding testosterone levels and other variables. Finally, we do not have data regarding SHBG, which would have given us the opportunity to study estimates of free and bioavailable testosterone in this population.

Despite a lack of mortality prognostication in our study, testosterone levels were associated in multivariate analysis with other risk markers, including albumin (taken here as a surrogate indicator of inflammation/malnutrition), BMI, and triglycerides. A strong negative correlation with CRP levels was also observed, altogether agreeing with the findings of the Swedish report (16) and implicating low testosterone levels with a less favorable phenotype. Of note, BMI arose as the strongest determinant of testosterone in our population. Such observation agrees with previous reports in nonrenal populations (28–30) and is consistent with the hypothesis that obesity, *via* direct leptin action (31) or adipocyte synthesis of aromatase enzyme (32), is able to suppress testosterone production. As a consequence, obese people have less muscle mass (33). Whether the hyperleptinemia observed in HD (34) may further contribute to testosterone deficiency is a hypothesis that merits further attention.

Conclusions

Even if our results indicate that testosterone is not an independent risk factor for mortality, available evidence indicates that increasing testosterone levels may improve other pathophysiologic pathways that are related to the elevated mortality risk of HD patients, such as nutritional status (35,36) and anemia (37), and further insight into the role of this hormone in men who are on HD may increase the interest of therapeutic restoration of testosterone deficiency in these patients.

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Disclosures

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