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Serum testosterone concentrations in male patients with end-stage kidney disease treated with haemodialysis

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Abstract

Introduction: Testosterone deficiency is frequently found in male patients with chronic kidney disease (CKD) and may participate in the pathogenesis of osteoporosis, sarcopaenia, anaemia, impotence, infertility, and other comorbidities observed in these patients. The aim of the study was the evaluation of the frequency of testosterone deficiency in male patients with CKD on maintenance haemodialysis (HD).
Material and methods: In 79 male HD patients, serum total (TT), free (FT) testosterone, C-reactive protein (CRP), and interleukin 6 (IL-6) serum concentrations were assessed before HD procedure. Patients were divided into three subgroups based on age categories: 19–39 years (18 patients), 40–59 years (34 patients), and ≥ 60 years (27 patients). TT insufficiency and deficiency were diagnosed when the serum TT concentration was below 4.0 ng/mL and 2.9 ng/mL, respectively. FT deficiency was diagnosed in patients with serum FT concentration below 8.9, 6.6, and 4.9 pg/mL in the abovementioned age subgroups, respectively.
Results: In the abovementioned age subgroups the serum TT concentration was 5.9 (4.6–7.1), 4.8 (3.9–5.4), and 4.6 (3.9–5.3) ng/mL, respectively. The serum FT concentration was 7.9 (5.2–10.1), 6.1 (5.1–7.2), and 6.0 (5.0–7.1) pg/mL, respectively. In the whole group TT insufficiency was found in 40%, TT deficiency in 15% of patients, and FT deficiency in 50% of patients. Significant negative correlations were found between both serum TT and FT concentrations and age ($r = –0.23$, $p = 0.05$ and $r = –0.27$, $p = 0.02$, respectively). Additionally, negative correlations were found between both serum TT and FT and IL-6 concentrations ($r = –0.43$, $p < 0.05$ and $r = –0.29$, $p < 0.05$), respectively.
Conclusions: 1. Testosterone deficiency is common in male patients with chronic kidney disease treated with HD. 2. In HD patients the serum testosterone concentration decreases with age. 3. Chronic inflammation may participate in the pathogenesis of testosterone deficiency in haemodialysis patients. **(Endokrynol Pol 2021; 72 (4): 347–352)**

Key words: *testosterone deficiency; hypogonadism; haemodialysis; end-stage kidney disease*

Introduction

Testosterone is a hormone that, in males, was originally associated primarily with sexual functions (e.g. libido, potency, and semen production). Nevertheless, it also has many additional metabolic actions. Firstly, it increases the synthesis of erythropoietin and boosts the tissue iron bioavailability. Testosterone also contributes to osteogenesis and stimulates muscle growth.

Testosterone deficiency may cause several complications. The most frequent is sexual dysfunction. Hypogonadism is associated with decreased libido, and impaired sexual function in men (ejaculatory and erectile dysfunction) [1, 2]. In a study by Araujo et al. it was reported that in men from the general population with TT < 300 ng/dL and FT < 5 ng/dL, low libido and erectile dysfunction occurred in 26% and 36%, respectively [2]. In men, testosterone deficiency may be linked to the development of osteoporosis, anaemia, and reduced muscle mass (sarcopaenia). Also, in these patients, abnormalities in body composition occur: the fat volume increases and the muscle mass is lowered [1, 3]. It has been observed that testosterone deficiency is associated with increased cardiovascular risk in the general male population [1]. Moreover, results of recent studies show that testosterone deficiency is linked to being frail or becoming frail in one year, as well as physical dysfunction in men on chronic haemodialysis [4].

In the general population testosterone deficiency is usually associated with aging and is observed in 6–10% of men (40–75 years old) [4]. Many chronic diseases, e.g. diabetes mellitus type 2, obesity, metabolic syndrome, depression, rheumatoid flares, hypertension, and chronic kidney disease, result in decreased serum testosterone concentration [2, 5, 6, 7]. Moreover, result of a recent study documented that low serum testosterone concentration is a risk factor of CKD progression in the male population [8].

In men with CKD the serum testosterone concentration decreases with the deterioration of kidney function and is the lowest in patients receiving renal replacement therapy. In the study by Carrero et al. a 44% prevalence of total testosterone (TT) deficiency (serum TT concentration < 2.9 ng/mL) among haemodialysis patients

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was observed, whereas TT insufficiency (serum TT concentration 2.9–4.0 ng/mL) was observed in 33% of patients. Only 23% of haemodialysis men had normal serum TT concentration (> 4.04 ng/mL) [3].

The low serum testosterone concentration in haemodialysis men may be caused by dysfunction of the hypothalamic–pituitary–testicular axis: impaired GnRH secretion, luteinizing hormone (LH) and follicle stimulating hormone (FSH) accumulation, increased serum prolactin (PRL), and reduction of 5-α reductase activity. The aforementioned abnormalities lead to an inappropriate signalling for the Leydig cells to produce testosterone [9–12]. What is more, it has been shown that in haemodialysis men with secondary hyperparathyroidism, treatment with cinacalcet may contribute to the decrease of serum TT and FT concentration [13]. The results of observational studies suggest that low serum testosterone concentration is correlated with higher mortality in haemodialysis patients [12].

In humans two testosterone fractions can be distinguished. The bioavailable, bioactive testosterone fraction, which contains free testosterone (FT), and testosterone bound to albumin. In contrast, testosterone bound with sex hormone-binding globulin (SHBG) is not active. The total amount of serum testosterone is described as the serum total testosterone concentration (TT) [1].

Taking into consideration , the severe consequences of testosterone deficiency, the frequent occurrence of endocrine disturbances in haemodialysis CKD patients, and the high mortality in this group of patients, as presented above, it seemed reasonable to investigate the prevalence of TT and FT deficiency in CKD men on maintenance haemodialysis.

Material and methods

Seventy-nine adult, haemodialysis male CKD patients were enrolled in this study. Tye mean age of patients was 54.0 (51.5–57.5) years. In all patients, serum TT, FT, SHBG, interleukin 6 (IL-6), C-reactive protein (CRP), and albumin concentrations were assessed. Blood samples were collected before a haemodialysis session in the middle of the week, two days after preceding dialysis session. Blood samples after collection were centrifuged and then frozen at –70°C until assay was done. Serum albumin, CRP, and IL-6 concentrations were assessed with an ELISA kit (albumin — Assaypro LLC, St. Charles, MO, USA; CRP — Immundiagnostik AG, Bensheim, Germany; IL-6 [hs] — R&D Systems, Abbinton, United Kingdom). Serum TT and FT concentrations were assessed with radioimmunoassay and SHBG with an IRMA technique (DIAsource Immunoassays, Nivelles, Belgium).

Patients were divided into three age subgroups: 19–39 years (18 patients), 40–59 years (34 patients), and ≥ 60 years (27 patients). TT insufficiency and deficiency were diagnosed, according to the recommendation of the Endocrine Society [14], when serum TT concentration was below 4.0 and 2.9 ng/mL, respectively. FT deficiency was diagnosed in patients with serum FT concentration below 8.9, 6.6, and 4.9 pg/mL in the abovementioned age subgroups, respectively.

Statistical analyses were done using the Statistica 10.0 PL software (StatSoft Polska, Cracow, Poland). ANOVA was used to assess differences in serum testosterone concentration between age subgroups, and chi-square to assess differences in the frequency of testosterone deficiency and insufficiency incidence. Correlation coefficients were calculated using Spearman's rank correlation. To reduce the possibility of an incidental nature of the obtained significant correlations, the multiple regression models were calculated with the serum FT and TT concentrations as dependent variables and factors that reached significance in correlation analyses as independent variables (i.e serum CRP and IL-6 concentrations and the patients' age). The results are presented as means with 95% confidence interval (CI); differences were considered significant when $p < 0.05$.

Results

The mean serum TT concentration in the whole study group was 4.92 ng/mL. In the patients' age subgroups analyses a significantly lower serum TT concentration was found in the oldest patients compared to the youngest group (Tab. 1).

The mean serum FT concentration in the whole study group was 6.64 pg/mL. In the patients' age subgroup analyses a significantly lower serum FT concentration was also found in the oldest patients compared to the youngest group (Tab. 1). Serum concentrations of IL-6, CRP, and SHBG in the studied group are presented in Table 2.

In the whole group TT insufficiency (2.9–4.0 ng/mL) and deficiency (< 2.9 ng/mL) were found in 25% and 15% patients, respectively (cumulatively 40% of patients had abnormal serum TT concentration). Abnormal serum TT concentration (both TT insufficiency and deficiency) was found in 24% of patients in the youngest age subgroup, in 42% of patients in the intermediate age subgroup, and in 46% of patients in the oldest age subgroup (the differences were not significant statistically: χ^2 $p = 0.15$). TT deficiency was found in 18% of patients

Table 1. *Serum total (TT) and free (FT) testosterone concentrations in maintenance haemodialysis males in age subgroups*

	Patients' age [years]		
	18–39 (n = 18)	40–59 (n = 34)	> 60 (n = 27)
TT concentration [ng/mL]	5.9 (4.6–7.1)	4.8 (3.9–5.4)	4.6 (3.9–5.3)*
FT concentration [pg/mL]	7.9 (5.2–10.1)	6.1 (5.1–7.2)	6.0 (5.0–7.1)*

*$p < 0.05$ *vs*. patients in the age group 18–39 years

Table 2. *Serum interleukin 6 (IL-6), C-reactive protein (CRP), and sex hormones binding globulin (SHBG) concentrations in maintenance haemodialysis males*

	Mean	95% CI
IL-6 [pg/mL]	7.44	6.33–8.57
CRP [mg/L]	11.09	9.71–12.47
SHBG [mmol/L]	28.90	25.44–32.35

CI — confidence interval

in the first subgroup, 16% in the second subgroup, and 12% in the third subgroup (the differences were also not significant statistically: chi^2 p = 0.74).

FT deficiency was found in 50% of patients. In the patients age subgroups FT deficiency was found in 78%, 56%, and 26%, respectively. Testosterone insufficiency was significantly more frequent in young patients (chi^2 p = 0.01)

A significant negative correlation was found between both serum TT and FT concentrations and age (r = –0.23, and r = –0.27, p < 0.05) (Fig. 1, 2), respectively. Moreover, significant inverse correlations were found between both TT and FT and IL-6 (r = –0.43, p < 0.05 and r = –0.29, p < 0.05) (Fig. 3, 4), respectively. A borderline significance correlation was found between serum TT and urea concentrations (r = 0.21; p = 0.09). There were no significant correlations between serum TT and FT concentration and serum CRP, PTH, albumin, and SHBG concentration, nor the patients' age.

In the multiple regression analysis, the serum FT concentration was inversely explained by the serum IL-6 concentration ($r_{partial}$ = –0.27; p = 0.01) and patients' age ($r_{partial}$ = –0.25; p = 0.03). The serum TT concentration was inversely explained by the serum IL-6 concentration ($r_{partial}$ = 20.43; p=0.002).

Discussion

In the current study, we have found a high prevalence of testosterone deficiency in patients on maintenance haemodialysis. This is in agreement with the results of previous studies in which the percentage of men with hypogonadism reached as much as 57% in men with CKD stage 5 [5, 15, 16].

In the current study we have found in that in patients on maintenance haemodialysis both serum TT and FT concentrations decrease with age. Other studies concerning this issue yielded similar results [5, 15, 16]. It is not yet clear why such a high percentage of CKD patients develop hypogonadism. Most likely the disturbances in the hypothalamic-pituitary-gonadal axis are the most important contributing component [17, 18]. Also, the direct damage to the Leydig cells caused by uraemia [18, 19] and the impact of different medications [13] must be taken into consideration as factors causing low testosterone concentrations in men with CKD. A surprising finding of the current study is that testosterone deficiency is more frequent in the group of younger patients than in the elderly. This

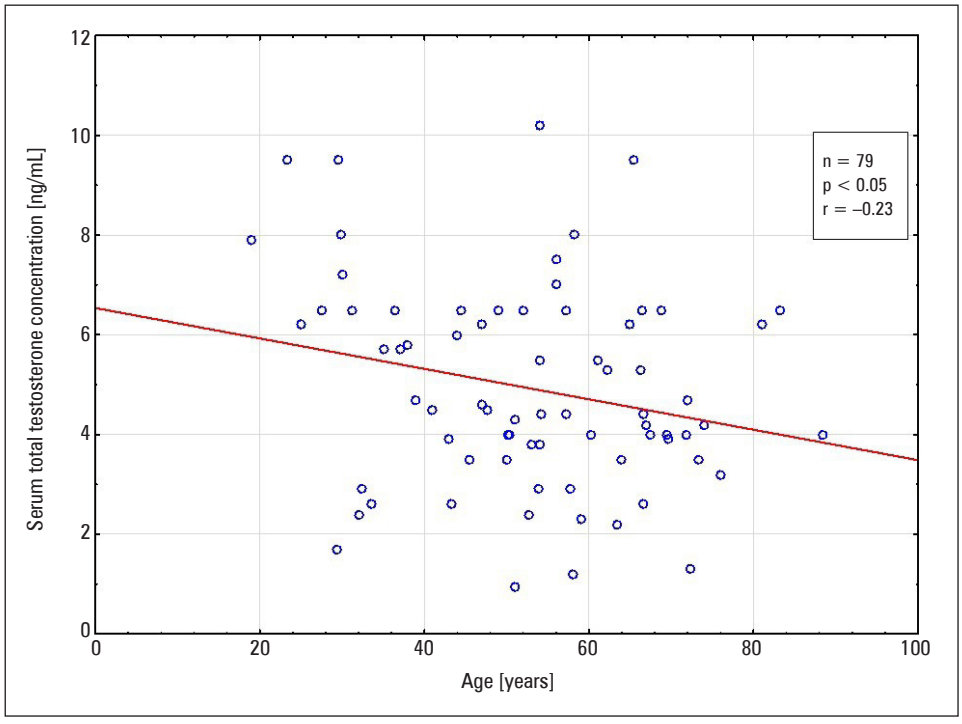

Figure 1. *Negative correlation between serum total testosterone concentration and age*

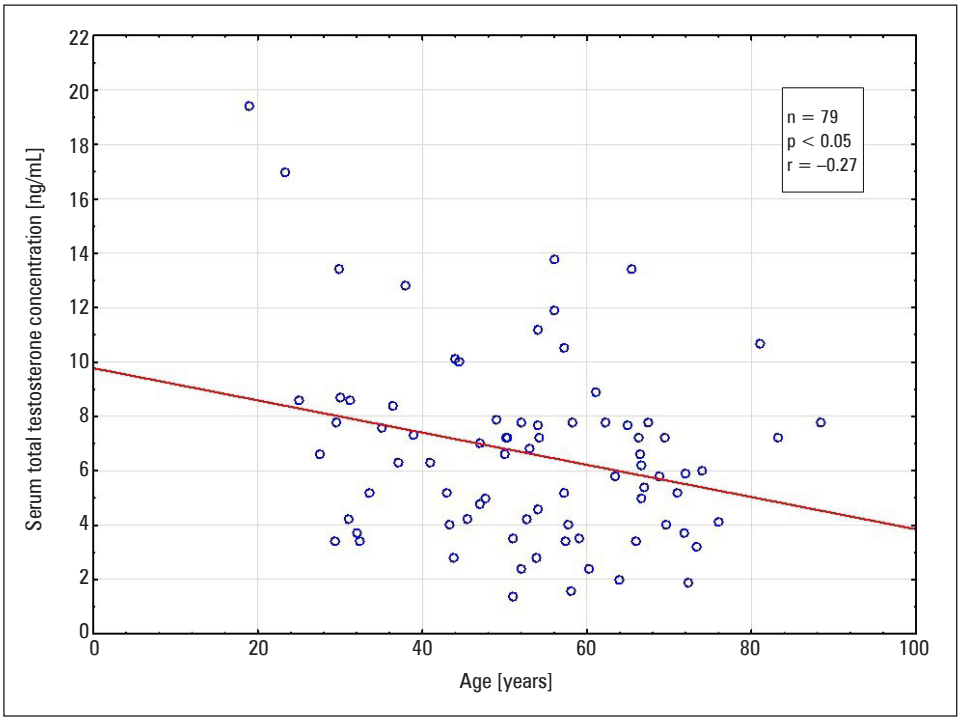

Figure 2. *Negative correlation between serum free testosterone and age*

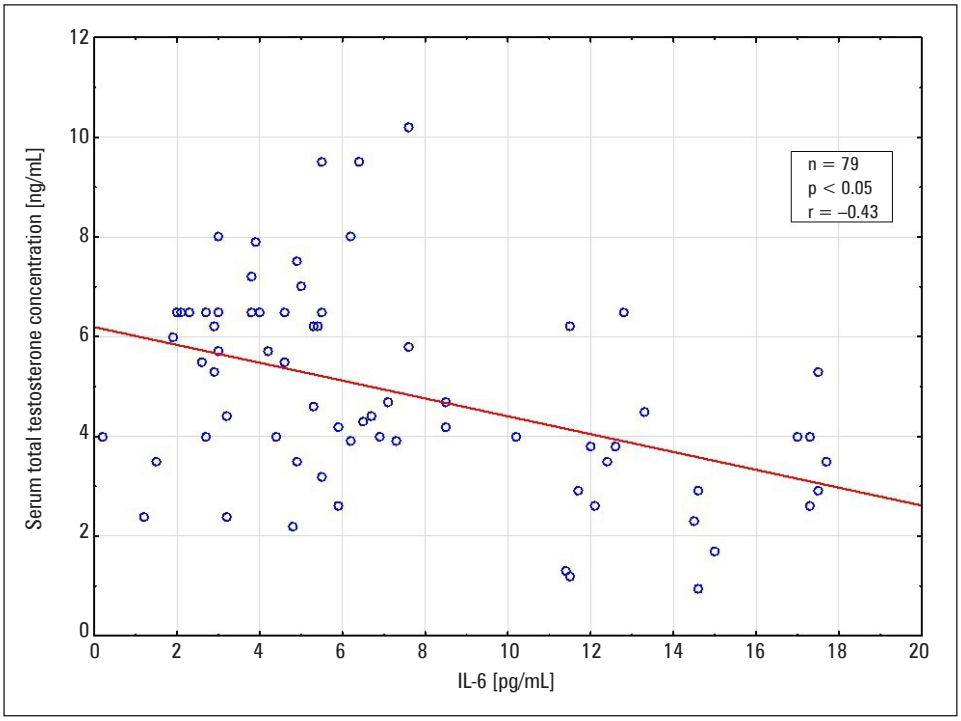

Figure 3. *Negative correlation between serum total testosterone and interleukin 6 (IL-6) concentration*

may be explained by the different cut-off points for the diagnosis of FT deficiency in different age groups. It is important to stress that there are no universal normal values of FT plasma concentration in the endocrinological guidelines. The clinical significance of this finding needs further elucidation, but there are more and more data available suggesting that low testosterone plasma concentration levels may be one of the causes of increased mortality in men with CKD and treated with RRT [8, 15].

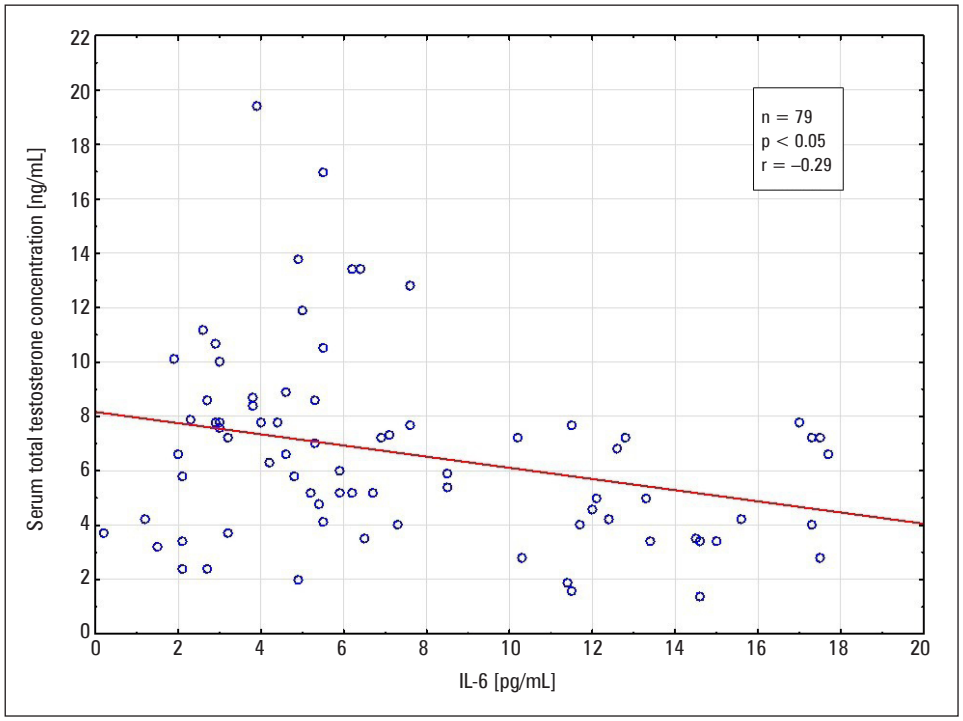

Figure 4. *Negative correlation between serum free testosterone and interleukin 6 (IL-6) concentration*

The mean serum concentration of serum SHBG in our study group (Tab. 2) was similar to the concentrations obtained by Hylander et al. [21], who analysed men with CKD stages 1–5, suggesting that SHBG is not related to the magnitude of kidney damage nor the use of renal replacement therapy.

Moreover, in the current study, we have found a significant inverse correlation between the marker of inflammatory status (serum IL-6 concentration) and serum concentration of both FT and TT. Taking into consideration the cross-sectional character of the current study, we have built multiple regression models to assess a more causal character of the observed relations. The TT concentration was inversely explained by serum IL-6 concentrations, and FT levels by both IL-6 concentration and age. This finding is, in general, in concordance with the results of previous studies [5, 15, 16]; however, we have found only the relation between IL-6 and TT of FT, while Carrero et al. observed strong correlation between serum testosterone concentration and another inflammatory marker – C-reactive protein. The differences may be explained by different tests used for the assessment, and the fact that the mean CRP values in both studies were not very high — 11 mg/L in our study and 6–16 mg/L (depending on the group) in the study by Carrero et al. This falls into the diagnosis of microinflammation rather than an overt inflammatory process. There are only a few studies published concerning the interrelation of microinflammation and testosterone plasma concentration in men. It was shown that in diabetic patients [22] testosterone concentration is also inversely related to the serum CRP and IL-6 concentrations; however, testosterone replacement therapy did not have an impact on the concentration of these cytokines. On the other hand, the results of a recent study by Dudek et al. [23] showed a significant decrease of serum CRP concentration in men with age-related hypogonadism treated with testosterone replacement therapy compared to placebo. Results of experimental studies suggest that testosterone may attenuate the secretion of inflammatory cytokines and thus protect the kidney against the ischemia-reperfusion damage [24]. This might explain the faster CKD progression in men with low serum testosterone concentration observed by Amri et al. [12]. It seems that testosterone has anti-inflammatory properties, as recently described by Bianchi [25]. It should be also mentioned that in some preliminary clinical studies it was shown that ESA treatment increased plasma testosterone concentrations in haemodialysis patients [26, 27].

Our study has some limitations. The most important is the retrospective, cross-sectional nature of our analyses, which precludes drawing firm conclusions of causality of the obtained results. The studied population was also not very large.

Conclusions

In the current study a significant decrease of serum TT and FT was observed in the elderly population; nev-

ertheless, testosterone deficiency was more frequently diagnosed in younger patients. Moreover, hypogonadism seems to be related to the inflammatory status of the male haemodialysis patients.

Conflict of interests

Nothing to declare.

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Disclosure statement

The results presented in this paper have not been published previously in whole or in part, except in abstract format. The authors declare no conflicts of interest for this study.

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