

Original Paper

Changes of Serum Total and Free Testosterone Concentrations in Male Chronic Hemodialysis Patients with Secondary Hyperparathyroidism in Response to Cinacalcet Treatment

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Key Words

Secondary hyperparathyroidism • Cinacalcet • Testosterone

Abstract

Background/Aims: Calcium sensing receptor (CaSR) is expressed, among others also in testis. Cinacalcet binds to the CaSR, increases sensitivity of CaSR to serum calcium and is used in the treatment of secondary hyperparathyroidism (sHPT) in chronic hemodialysis patients (HDP). In most of male HDP, serum testosterone concentration is lower than in healthy males. The aim of this study was to assess the influence of six-month treatment with cinacalcet on the serum total and free testosterone concentration in male HDP with sHPT. **Methods:** 38 male, hemodialysed CKD patients with sHPT (PTH>300 pg/ml) were enrolled into the study. In each patient serum PTH, total testosterone (TT) and free testosterone (FT) concentrations were assessed before the first dose of cinacalcet and then after 3 and 6 months of treatment. The results are presented as means with 95% confidence interval. **Results:** In 33 patients who completed the study cinacalcet treatment caused significant decrease of serum PTH from 1143 pg/ml (828 - 1458 pg/ml) at the baseline, to 809 pg/ml (487 - 1132pg/ml) after 3 month of treatment ($p = 0.002$), and to 607 pg/ml (281 - 934pg/ml; $p < 0.0001$) after 6 months of treatment. Serum TT concentration also decreased from 4.95ng/ml (4.23 - 5.67 ng/ml) to 4.45 ng/ml (3.85 - 5.06ng/ml) and to 4.39 ng/ml (3.75 - 5.03ng/ml), respectively (p for trend = 0.009). Moreover, serum FT concentration decreased from 6.95 pg/ml (5.54 - 8.36pg/ml) to 5.98 pg/ml (5.00-6.94 pg/ml); $p = 0.14$ and to 5.60 pg/ml (4.63 - 6.57 pg/ml); $p = 0.034$, respectively (p for trend = 0.012). **Conclusion:** Treatment with cinacalcet decreases serum total and free testosterone concentration in male hemodialysed patients with chronic kidney disease and secondary hyperparathyroidism.

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Introduction

Since the introduction of cinacalcet in the year 2004 secondary hyperparathyroidism (sHPT) can be treated with calcimimetics. These compounds bind to the calcium sensing receptor (CaSR) what leads to its positive allosteric modulation. This results in increased sensitivity of CaSR to serum calcium and subsequently leads to the decrease of parathyroid hormone (PTH) production by the parathyroid glands [1, 2].

CaSR is a seven-transmembrane G-protein-coupled receptor. Its main function is to modulate PTH secretion in the parathyroid glands in response to serum calcium concentration changes [1, 3]. Recently, the expression of CaSR has been documented outside the parathyroid glands. CaSR is present among others in various endocrine organs e.g. the pituitary gland, hypothalamus [4], β cells of the pancreas [5] and testis [6].

In most male hemodialysed patients, plasma testosterone concentration is decreased [7, 8]. Recently, Carrero et al. [9] showed testosterone deficiency (serum total testosterone < 10 nmol/l which equals < 2.88 ng/ml) in 44% of the hemodialysis patients, while in 33% testosterone insufficiency (10 - 14 nmol/l which equals 2.88 - 4.04 ng/ml) was diagnosed. Only 23% patients in the studied group had normal testosterone levels (>14 nmol/l which equals > 4.04 ng/ml). Lowered serum testosterone concentrations in these patients may be caused by reduced synthesis, increased catabolism, or a combination of the aforementioned abnormalities.

Another important factor that may lead to hypogonadism in hemodialysed patients is malnutrition. It was shown, that in CKD patients on a low-protein diet, essential aminoacids and their ketoanalog supplementation raised low plasma testosterone concentration [10].

Androgen deficit in CKD males may lead to the changes of body composition. Body fat increases while lean body mass is reduced. Low serum androgens concentrations may contribute to reduced muscle mass (sarcopenia), osteoporosis, and high bone fracture incidence [9]. Additionally, androgen deficit also may impair libido and sexual function and might lead to depression [11]. Moreover, serum testosterone concentration is strongly and inversely correlated with inflammatory markers (e.g. serum CRP and IL-6) [9]. Finally, it was recently shown that low testosterone concentrations were associated with worse outcomes in male hemodialysis patients [7, 8].

Secondary sHPT itself might, at least partially, participate in the development of hypogonadism [10, 12]. It was shown, that parathyroidectomy in patients with sHPT leads to the improvement of sexual function and spermatogenesis [13, 14].

Although there is some information given in the manufacturers product characteristics that cinacalcet reduces serum TT and FT concentration there is no information whatsoever about the studied cohort of patients (e.g. age, sHPT severity) and no clinical trial confirming or abolishing this finding has been conducted. Thus this side-effect of cinacalcet treatment is generally overlooked by most clinicians.

Taking into consideration abovementioned lack of clinical studies, severe consequences of low serum testosterone concentration, the fact that CaSR – the target receptor for cinacalcet is expressed in testes, as well as suggested involvement of sHPT in the development of hypogonadism, it was reasonable to study the influence of cinacalcet treatment on serum total and free testosterone concentrations in male hemodialysed patients with chronic kidney disease and secondary hyperparathyroidism.

Materials and Methods

Thirty eight adult, hemodialysed, male CKD patients with sHPT (defined as serum PTH concentration > 300 pg/ml) were enrolled in this prospective, open-label, single arm study. Mean age of patients was 50.3 ± 14.3 years, median time of renal replacement therapy was 36 ± 49 months. Exclusion criteria were: age below 18 years, severe liver insufficiency, hypersensitivity to any of the study drug compounds, high probability of non-compliance and suspected short life expectancy on hemodialysis.

All patients were treated with cinacalcet. Initial dose was 30 mg once daily and was modified, if needed, every 4 weeks depending on the serum PTH concentration. The aim of treatment was to decrease serum PTH concentration to the target values: 150 - 300 pg/ml. Maximal dose of cinacalcet allowed in the study protocol was 120 mg daily.

The doses of intestinal phosphate binders (in all patients calcium carbonate was administered) and active vitamin D₃ analogues (in all patients alfacalcidol was administered) were flexible in order to avoid cinacalcet related hypocalcemia and hypophosphatemia. Aluminum hydroxide was only used as a temporary "rescue" therapy in patients with severe hyperphosphatemia.

In all patients serum total testosterone (TT), free testosterone (FT), sex hormone binding globulin (SHBG), PTH, interleukin-6 (IL-6), C-reactive protein (CRP), albumin, calcium, and phosphate concentrations were assessed before the first dose of cinacalcet and then after 3 and 6 months of treatment. Blood samples were collected before hemodialysis session in the middle of the week. After collection blood samples were centrifuged, serum was aliquoted in 1ml test-tubes and then rapidly frozen in -70°C. Serum PTH concentration (intact PTH) was assessed using electrochemiluminescence (ECL) technique (Roche, Mannheim, Germany). Serum albumin, CRP and IL-6 concentration was assessed with an ELISA (albumin – Assaypro LLC, St. Charles, MO, USA; CRP – Immundiagnostik AG, Bensheim, Germany; IL-6 (hs) – R&D Systems, Abingdon, United Kingdom). Serum TT and FT concentrations were assessed with radioimmunoassay and SHBG with an IRMA technique (DIAsource Immunoassays, Nivelles, Belgium). Serum calcium and phosphate concentration was assessed using the Beckman-Coulter UniCel DxC 600 analyser and blood hemoglobin concentration using standard procedures of the University Hospital's central laboratory.

Statistical analyses were performed using the Statistica 10.0 PL software (StatSoft Polska, Cracow, Poland). Kolmogorov–Smirnov test was used to test the variables distribution. Repeated measures ANOVA with Bonferroni correction for multiple comparisons test was used to assess changes of variables over time and chi² test to assess the differences in qualitative variables. Correlation coefficients were calculated according to Spearman. Additionally multivariate regression analyses were performed to assess the factors that influenced baseline serum TT and FT concentrations and the magnitude of their changes over time.

Results are shown as means with 95% confidence index (CI), means with standard deviation, or median values with standard deviation when appropriate. Differences were considered significant when $p < 0.05$. The study protocol, adherent to the Declaration of Helsinki, was approved by the Ethics Committee of Medical University of Silesia (KNW/0022/KB1/56/I/10 - 21.09.2010) and all patients gave written informed consent for participation in the study, before enrollment.

Results

From 38 enrolled patients, 33 (mean age 51.4 ± 14.9 years) completed the study. Among 5 patients who were ruled out of the study one patient died, one received kidney allograft, one patient discontinued the study because of permanent decrease of serum PTH concentration below 150 pg/ml, one underwent parathyroidectomy, and one was transferred to a distant dialysis center.

Mean daily doses of cinacalcet after 3 and 6 months of treatment were 45 ± 19 mg and 51 ± 21 mg, respectively. The highest administered dose of cinacalcet was 90 mg/day. The doses of intestinal phosphate binders and active vitamin D₃ analogues were flexible in order to avoid hypocalcemia and hypophosphatemia related to cinacalcet treatment. The percentage of patients treated with alfacalcidol and mean daily dose of alfacalcidol were stable (Table 1).

There was an increase of mean daily dose of calcium carbonate during the observation period. The percentage of patients treated with calcium carbonate did not change significantly. Moreover, there was a significant decrease in the mean dose of aluminum hydroxide after 6 months of treatment. The number of patients treated with aluminum hydroxide did not change significantly (Table 1).

In patients who completed the study cinacalcet treatment caused significant decrease of serum PTH after 3 and 6 months (Table 1). The mean decrease of serum PTH concentration after 3 and 6 months of treatment was 29.3% and 46.1% respectively.

Table 1. Doses of alfacalcidol, intestinal phosphate binders and serum/plasma concentrations of PTH, calcium, phosphate, free testosterone, total testosterone, SHBG, IL-6, CRP, albumin and blood hemoglobin concentration the study group during cinacalcet treatment. PTH-parathyroid hormone. CRP-C-reactive protein. SHBG- sex hormone binding globulin. IL-6-Interleukin 6. * $p < 0.05$ vs baseline

	At the baseline	After 3 months of treatment	After 6 months of treatment	<i>p</i> for trend
Dose of alfacalcidol [mcg/24h]	0.27 (0.15-0.40)	0.33 (0.18-0.48)	0.41 (0.21-0.61)	0.13
Number of patients treated with alfacalcidol	18 (55%)	21 (64%)	24 (73%)	0.15
Dose of CaCO ₃ [g/24h]	3.6 (2.5-4.7)	4.1 (3.0-5.3)	4.2* (3.2-5.3)	0.015
Number of patients treated with CaCO ₃	29 (88%)	31 (94%)	31 (94%)	0.18
Dose of aluminum hydroxide [mg/24h]	550 (215-850)	410 (50-770)	180* (-40-400)	0.016
Number of patients treated with aluminum hydroxide	10 (30%)	6 (18%)	3 (9%)	0.09
PTH [pg/ml]	1143 (828-1458)	809* (487-1132)	607* (281-934)	< 0.001
Calcium [mmol/l]	2.19 (2.08-2.29)	2.07 (1.97-2.16)	2.12 (2.02-2.22)	0.25
Phosphate [mmol/l]	2.08 (1.89-2.26)	2.10 (1.87-2.34)	1.98 (1.74-2.22)	0.39
Total testosterone [ng/ml]	4.95 (4.23-5.67)	4.45 (3.85-5.06)	4.39* (3.75-5.03)	0.028
Free testosterone [pg/ml]	6.95 (5.54-8.36)	5.98 (5.00-6.94)	5.60* (4.63-5.67)	0.012
SHBG [nmol/l]	26.8 (20.7-32.8)	28.0 (22.9-33.1)	28.8 (23.9-33.7)	0.42
IL-6 [pg/ml]	6.59 (5.20-7.98)	6.29 (4.93-7.65)	6.40 (5.20-7.59)	0.79
CRP [mg/l]	12.8 (10.6-15.1)	11.8 (9.2-14.4)	10.7 (8.49-12.9)	0.12
Albumin [mg/ml]	67.4 (59.5-75.4)	62.3 (54.5-70.0)	64.0 (56.4-71.6)	0.53
Hemoglobin [g/dl]	10.92 (10.50-11.35)	10.95 (10.42-11.47)	10.99 (10.60-11.37)	0.80

In the entire study group there were no significant differences in the mean serum calcium and phosphate concentration during cinacalcet treatment (Table 1). As shown in Table 1, six months treatment with cinacalcet led to a significant decrease in the mean TT and FT concentrations. Serum SHBG concentration was stable during the treatment period (Table 1). There were no significant changes in the mean concentration of inflammatory markers during cinacalcet therapy (Table 1). Also, serum albumin concentration remained stable during the treatment period (Table 1).

During the cinacalcet treatment a tendency to the increase in the prevalence of testosterone insufficiency (serum total testosterone concentration 2.88 - 4.04 ng/ml) from 30% (10 patients) at the baseline to 42% (14 patients) after 3 months of treatment and 52% (17 patients) after 6 months of treatment (borderline significance – $p = 0.08$) was observed. The increase in the prevalence of testosterone deficiency (serum testosterone concentration < 2.88 ng/ml) was not significant – 15% (5 patients), 24% (8 patients) and 21% (7 patients); $p = 0.37$, respectively.

Correlation analyses

There was a significant positive correlation between the baseline serum concentration of total and free testosterone and the baseline concentration of IL-6 ($R = -0.52$; $p = 0.002$ and $R = -0.55$; $p = 0.001$, respectively). Moreover, there was a significant inverse correlation between the baseline FT concentration and the time of renal replacement therapy ($R = -0.45$; $p = 0.01$). There were no significant correlations between neither serum TT and FT concentration and serum CRP, PTH, albumin, blood hemoglobin concentration nor the patients' age.

There was a significant positive correlation between the change of serum TT concentration and the change of serum PTH concentration after both 3 and 6 months of treatment (Table 2). Moreover, after 6 months of treatment significant positive correlation

Table 2. Correlation coefficients (univariate) between the changes (0-3 months and 0-6 months) of serum total and free testosterone concentrations and selected variables. PTH-parathyroid hormone. SHBG - sex hormone binding globulin. CRP - C-reactive protein. IL - 6-interleukin 6

	the change of total testosterone 0-3 months [ng/ml]	the change of free testosterone 0-3 months [pg/ml]		the change of total testosterone 0-6 months	the change of free testosterone 0-6 months
the change of PTH 0-3 months [pg/ml]	0.53; p=0.002	0.06; p=0.75	the change of PTH 0-6 months [pg/ml]	0.45; p=0.01	0.26; p=0.15
cinacalcet dose at 3 months [mg]	0.05; p=0.77	-0.26; p=0.14	cinacalcet dose at 6 months [mg]	0.37; p=0.036	-0.03; p=0.88
the change of IL-6 0-3 months [pg/ml]	-0.36; p=0.054	-0.22; p=0.2	the change of IL-6 0-6 months [pg/ml]	-0.39; p=0.02	-0.31; p=0.09
the change of CRP 0-3 months [mg/l]	-0.03; p=0.86	0.29; p=0.11	the change of CRP 0-6 months [mg/l]	-0.06; p=0.73	0.21; p=0.25
the change of SHBG 0-3 months [nmol/l]	0.23; p=0.20	0.05; p=0.8	the change of SHBG 0-6 months [nmol/l]	0.45; p=0.008	0.14; p=0.44

Table 3. Multiple regression analyses of the serum baseline concentration of total and free testosterone and selected variables. PTH-parathyroid hormone. CRP-C-reactive protein. IL-6-interleukin 6. BMI-body mass index

	Baseline total testosterone concentration [pg/ml]			Baseline free testosterone concentration [ng/ml]		
	β	Standard error	p	β	Standard error	p
Age [years]	0.04	0.17	0.81	-0.11	0.16	0.52
Hemodialysis vintage [months]	-0.27	0.16	0.11	-0.458	0.16	0.007
Baseline PTH concentration [pg/ml]	0.21	0.16	0.20	-0.05	0.15	0.76
Baseline CRP concentration [mg/l]	-0.05	0.16	0.73	0.18	0.15	0.24
Baseline IL-6 concentration [pg/ml]	-0.47	0.17	0.01	-0.48	0.16	0.006
BMI [kg/m ²]	-0.20	0.16	0.23	0.27	0.16	0.27

between the change of TT and cinacalcet dose (Table 2) and also significant inverse correlation between the change of serum TT and change of serum IL-6 was found (Table 2). The correlation between change of serum FT and the change of serum IL-6 concentration had borderline significance (p = 0.09 – Table 2).

Multiple regression analyses

Due to several significant correlations additional analyses of multiple regression were performed for more precise assessment of the relations between variables. Baseline serum concentrations of TT and FT, as well as the change of serum TT and change of serum FT concentrations after 3 and 6 months were chosen as the dependent variables.

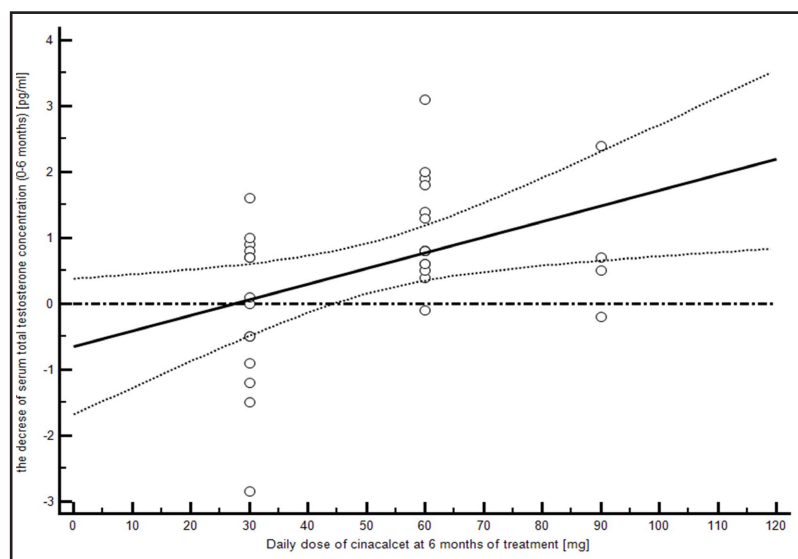
The baseline concentration of TT was inversely explained by the serum IL-6 concentration and not by the age, hemodialysis vintage, BMI, nor the baseline serum concentrations of PTH and CRP (Table 3). The baseline concentration of FT was inversely explained by the serum IL-6 concentration and hemodialysis vintage and not the age, BMI, nor the baseline serum concentrations of PTH and CRP (Table 3)

The change of serum TT after 3 months of treatment with cinacalcet was explained by the change of the serum PTH concentration (Table 4). The change of serum TT after 6 months of treatment was explained by the dose of cinacalcet (Fig. 1) and inversely by the change of serum IL-6. The change of serum FT after 6 months of treatment was inversely explained by the change of serum IL-6 (Table 4).

Table 4. Multiple regression analyses of the changes (0-3 months and 0-6 months) of serum concentration of total and free testosterone and the changes of selected variables. PTH-parathyroid hormone. CRP-C-reactive protein. IL-6-interleukin 6

	the change of total testosterone concentration 0-3 months [pg/ml]			the change of free testosterone concentration 0-3 months [ng/ml]				the change of total testosterone concentration 0-6 months [pg/ml]			the change of free testosterone concentration 0-6 months [ng/ml]		
	β	Standard error	p	β	Standard error	p		β	Standard error	p	β	Standard error	p
Cinacalcet dose at 3 months [mg]	-0.06	0.20	0.74	-0.34	0.20	0.10	Cinacalcet dose at 6 months [mg]	0.38	0.15	0.02	-0.15	0.17	0.41
the change of PTH concentration 0-3 months [pg/ml]	0.43	0.18	0.02	0.13	0.19	0.52	the change of PTH concentration 0-6 months [pg/ml]	0.28	0.16	0.09	-0.02	0.18	0.90
the change of CRP concentration 0-3 months [mg/l]	0.18	0.19	0.35	0.44	0.20	0.13	the change of CRP concentration 0-6 months [mg/l]	0.23	0.16	0.16	0.28	0.18	0.14
the change of IL-6 concentration 0-3 months [pg/ml]	-0.30	0.18	0.10	-0.31	0.18	0.10	the change of IL-6 concentration 0-6 months [pg/ml]	0.34	0.17	0.049	-0.43	0.19	0.03

Fig. 1. The correlation between the decrease of serum total testosterone concentration and the dose of cinacalcet after 6 months of treatment.



Discussion

In the current clinical study we have observed a significant decrease of both serum total, and free testosterone concentrations in hemodialysed patients with CKD and sHPT after six-month treatment with cinacalcet. These decreases were related to the decrease of serum PTH concentration, the dose of cinacalcet and the changes of inflammatory markers concentrations. Also, a tendency to the increase in the prevalence of testosterone insufficiency was observed.

Cinacalcet was introduced in the year 2004 and has been proven to be effective in the treatment of secondary hyperparathyroidism [15, 16] and other morbidities e.g. calciphylaxis [17]. Nevertheless, to the best of our knowledge, no clinical study concerning the influence of cinacalcet on serum total and/or free testosterone concentration has been published so far.

As it was mentioned above, there is some information given in the manufacturer's product characteristics concluding that in patients treated with cinacalcet serum TT concentration decreased by a median of 15.8% while the decrease was only by 0.6% in the

placebo-treated patients. Serum FT concentration decreased by a median of 31.3% in the patients treated with cinacalcet and by 16.3% in the placebo-treated patients [18]. This was even a more pronounced decrease than in our study (the decrease of serum TT and FT concentrations was 11.4% and 19.4%, respectively). This discrepancy could be, at least up to a point, explained by the differences in the patients' age, as well as baseline serum PTH concentration, or the magnitude of serum PTH decrease after cinacalcet treatment. Nevertheless, to the best of our knowledge, such data concerning the aforementioned cohort are unavailable.

We have found a strong inverse correlation between the serum concentrations of both TT and FT and the serum concentration of inflammatory markers (especially IL-6). Also the magnitude of TT and FT decrease were inversely correlated with serum IL-6 concentration changes. This relation was further confirmed in the multiple regression analyses. These results are in agreement with previously conducted studies concerning the relation between inflammation and hypogonadism [9, 19].

Testosterone deficiency is associated with various co-morbidities such as: insulin resistance, type 2 diabetes mellitus, central adiposity, hypertension, inflammation, atherosclerosis and cardiovascular disease, erectile dysfunction and finally increased incidence of mortality [19, 20]. Therefore it is clinically important to assess the influence now commonly used pharmacological agents (e.g. cinacalcet) on serum testosterone concentration, especially in patients with initially decreased serum androgens concentrations – such as hemodialysed CKD patients. As it was shown in the current study, treatment with cinacalcet may lead to the increased prevalence of testosterone insufficiency and perhaps testosterone deficiency.

Our study has some limitations. The most important is the lack of placebo treated control group. Nevertheless, in a study by Molsted et al. it was shown that, in male maintenance hemodialysis patients, serum TT and FT concentration had not change during a 4-months observation period, in the absence of any testosterone-directed treatment [21]. Moreover, cinacalcet is nowadays commonly used in the treatment of sHPT, so conducting a placebo-controlled study with this agent raises some significant ethical issues.

Another drawback might be the relatively small sample size. Nevertheless, even in such small group significant correlations between the reduction of serum TT and FT concentrations with the decrease of serum PTH concentrations as well as the dose of cinacalcet were observed. These dependencies were further confirmed in the multiple regression analyses. Due to the aforementioned relatively low number of enrolled subjects the results of our study are obviously not definitive. In fact, this study was meant to generate a hypothesis worth further evaluation. The questions still to be answered are whether the decrease of serum TT and FT concentrations is related to the treatment with all calcimimetics or specifically only to cinacalcet and what is the clinical relevance of this finding.

Conclusion

We have found that six-month treatment with cinacalcet decreases serum total and free testosterone concentration in male hemodialysed patients with chronic kidney disease and secondary hyperparathyroidism. Such a decrease of serum TT and FT concentration was associated, among others, with the magnitude of serum PTH decrease and the dose of cinacalcet.

Disclosure Statement

Nothing to declare.

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