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Three months treatment with cinacalcet does not change plasma leptin concentration in hemodialysis patients with secondary hyperparathyroidism**

Trzymiesięczne leczenie cynakalcetem nie zmienia stężenia leptyny w osoczu u hemodializowanych chorych z wtórną nadczynnością przytarczyc

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Keywords

hemodialysis, secondary hyperparathyroidism, cinacalcet, leptin

Słowa kluczowe

hemodializoterapia, wtórna nadczynność przytarczyc, cynakalcet, leptyna

S u m m a r y

Introduction. Cinacalcet is a calcimimetic which increases the sensitivity of calcium sensing receptor (CaSR) to the serum calcium. CaSR is expressed among others also in adipocytes. Leptin is a hormone synthetized by the adipocytes which is involved in the regulation of energy balance and seems to be a marker of nutrition.

Aim. The aim of this study was to assess the influence of 3 months treatment with cinacalcet on plasma leptin concentration in hemodialysis patients (HDP) with secondary hyperparathyroidism (sHPT).

Material and methods. In 65 HDP with sHPT treated with cinacalcet (30-90 mg/day) serum parathyroid hormone (PTH) and plasma leptin concentrations were assessed before the first dose of cinacalcet and then after 3 months of treatment.

Results. During 3 month treatment with cinacalcet a significant decrease in serum PTH concentration was found: from 1089 (891-1286) pg/ml to 775 (574-976) pg/ml, respectively ($p < 0.0001$). There was no significant change of plasma leptin concentration after 3 months of treatment with cinacalcet: 30.4 (21.1-39.8) ng/ml and 33.7 (23.6-43.9) ng/ml, respectively.

Conclusions. Three months treatment with cinacalcet does not significantly influence the plasma leptin concentration in hemodialysis patients with sHPT.

S t r e s z c z e n i e

Wstęp. Cynakalcet jest kalcimimetykiem, czyli lekiem zwiększającym wrażliwość receptora wapniowego (CaSR) na wapń w surowicy. Ekspresja CaSR zachodzi między innymi w adipocytach. Leptyna jest hormonem wytwarzanym przez adipocyty, który jest związany z bilansem energetycznym ustroju. Jest ona również uważana za wskaźnik odżywienia.

Cel pracy. Celem niniejszego badania była ocena wpływu 3-miesięcznego leczenia cynakalcetem na stężenie leptyny w osoczu u hemodializowanych chorych (HDP) z wtórną nadczynnością przytarczyc (sHPT).

Materiał i metody. U 65 HDP z sHPT leczonych cynakalcetem (30-90 mg/dzień) oznaczano stężenia parathormonu (PTH) w surowicy oraz leptyny w osoczu. Próbki krwi były pobierane przed rozpoczęciem leczenia cynakalcetem i po 3 miesiącach powyższego leczenia.

Wyniki. Po 3 miesiącach leczenia zaobserwowano znamienne zmniejszenie stężenia PTH w surowicy z: 1089 (891-1286) pg/ml do 775 (574-976) pg/ml ($p < 0,0001$). Nie zaobserwowano natomiast znamiennych różnic w stężeniu leptyny w osoczu (wynosiło ono odpowiednio: 30,4 (21,1-39,8) ng/ml i 33,7 (23,6-43,9) ng/ml ($p = 0,063$)).

Wnioski. Trzymiesięczne leczenie cynakalcetem nie wpływa znamiennie na stężenie leptyny w surowicy u chorych hemodializowanych z wtórną nadczynnością przytarczyc.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

In the last decade new pharmacological agents – the calcimimetics have been added to the armamentarium of treatment of hemodialysis patients with secondary hyperparathyroidism (sHPT). The calcimimetics bind to calcium sensing receptor (CaSR) leading to its positive allosteric modulation, what results in the increased sensitivity of CaSR to serum calcium thus leading to

**This paper is dedicated to Professor Franciszek Kokot – our outstanding teacher and mentor.

the decrease of parathormone (PTH) secretion by the parathyroid glands (1, 2). Cinacalcet is mostly used in the treatment of sHPT in patients with chronic kidney disease (CKD) stage 5, who require renal replacement therapy.

Results of many clinical studies in hemodialysis patients with sHPT suggest that treatment with cinacalcet with addition of small doses of active vitamin D analogues is efficient in reducing the serum PTH concentration and causes more pronounced reduction in the progression of cardiovascular and heart valve calcification, than treatment with vitamin D analogues alone (3-5). However, it should be mentioned, that the result of the EVOLVE study did not confirm the improvement of the cardiovascular prognosis of hemodialysed CKD patients with sHPT treated with cinacalcet (6).

Calcium sensing receptor (CaSR) is a seven-transmembrane G-protein-coupled receptor. It's main function is to modulate the parathormone (PTH) secretion by the parathyroid glands in response to changes of serum calcium concentrations (1, 7). Recently the existence of CaSR has been described in a number of tissues besides the parathyroid glands.

CaSR expression has been documented among others in adipocytes (8, 9), in which CaSR stimulation leads to the decrease of lipolysis (10, 11) and an increase of adipogenesis (through the intensification of preadipocyte to adipocyte differentiation) (12). Additionally, CaSR stimulation increases the synthesis and secretion of proinflammatory cytokines such as: interleukin-6 (IL-6), interleukin-1 β or tumor necrosis factor α by the adipocytes (13). What is more we have described an increase of plasma concentration of another adipokine – adiponectin in chronic hemodialysis patients with sHPT as a result of cinacalcet treatment (19).

Leptin is a 16 kDa protein synthesized predominantly by adipocytes. Firstly leptin was regarded as a "satiety hormone" which down-regulates the neuropeptide Y (one of the most potent appetite regulating hormones) mRNA transcription in the hypothalamus. Nowadays leptin is considered mostly as a marker of nutrition, as its plasma concentration strictly reflects the total adipose tissue content and is markedly elevated in obese patients (14, 15). Kidney is the organ where majority of leptin is biodegraded and eliminated and thus plasma leptin concentration is significantly increased in patients with CKD and normalizes after successful kidney transplantation (16, 17).

Leptin directly stimulates the activity of sympathetic nervous system. Moreover, leptin receptors have been identified in the endothelium, platelets, and monocytes/macrophages. These properties of leptin seem to be involved in the negative impact of adipose tissue on the cardiovascular system in obese subjects. Additionally, increased plasma leptin concentration has been shown to be the independent (from the body mass) predictor of cardiovascular complications in the WOSCOPS Study (18).

As CaSR is expressed in adipocytes, stimulation of this receptor may influence the secretion of different adipokines and cytokines. It has been recently shown, that treatment with cinacalcet increases plasma adiponectin concentration (19). Therefore it seems reasonable to assess the influence of CaSR stimulation by calcimimetic on plasma leptin concentration (secreted mainly by adipocytes). Such a speculated additional effect of calcimimetics seems to be clinically important taking into consideration the potential harmful consequences of increased plasma leptin concentration (20) and could explain the potential beneficial impact of cinacalcet treatment on the cardiovascular morbidity and mortality suggested in some studies (4-6).

AIM

The aim of this study was to assess the influence of 3 months treatment with cinacalcet on plasma leptin concentration in hemodialysis patients with secondary hyperparathyroidism.

MATERIAL AND METHODS

Seventy one adult, hemodialysis patients with end stage kidney disease – ESKD (40 males and 31 females) and sHPT (serum PTH concentration > 300 pg/ml) recruited from 9 hemodialysis centers were enrolled in this prospective, open-label, single arm study. Mean age of patients was 53.3 (49.8-56.9) years, median vintage of dialysis was 32 months (interquartile range (IQR) – 28 months). Exclusion criteria were as follows: age below 18 years, severe liver insufficiency, oversensitivity to any of the study drug compounds, high probability of non-compliance and suspected short life expectancy.

All enrolled patients were treated with cinacalcet. Initial dose was 30 mg once daily and was modified, if necessarily, every 4 weeks accordingly with the serum PTH concentration. The target of treatment was to decrease serum PTH concentration to 150-300 pg/ml. Maximal allowed dose of cinacalcet was 120 mg daily.

The dosing of alfacalcidol and/or calcium carbonate was flexible in order to avoid hypocalcaemia and hypophosphatemia related to the cinacalcet treatment. The doses of abovementioned medications were titrated monthly, accordingly with the results of routine biochemical analyses.

As it was mentioned before serum PTH, calcium and phosphate concentrations were assessed in 1-month intervals in each hemodialysis unit in order to adjust the cinacalcet dose (data not presented in this manuscript). Moreover, in all patients, plasma leptin concentration, as well as serum PTH, calcium, phosphate and C-reactive protein (CRP) concentrations were assessed before the first dose of cinacalcet and then after 3 months of treatment in the central laboratory of the Department of Nephrology, Transplantation and Internal Medicine.

Blood samples were collected before hemodialysis procedure in the middle of the week. After collection,

blood samples were centrifuged, aliquoted and frozen in -70°C until assay. Serum intact-PTH concentration was assessed using electrochemiluminescence (ECL) technique (Roche, Mannheim, Germany), plasma leptin, and serum CRP concentrations were assessed with ELISA kits (Leptin – Linco Research, St. Charles, Missouri, USA, CRP – Immunodiagnostik AG, Bensheim, Germany). Serum calcium, and phosphate concentrations were assessed in the hospital's central laboratory using standard procedures (Beckman-Coulter UniCel DxC 600 analyser).

Statistical analyses were calculated using the Statistica 10.0 PL software (StatSoft Polska, Cracow, Poland). Shapiro-Wilk test was used to test the variables distribution, Wilcoxon matched pairs test and chi-square test were used to assess the changes between variables. Correlation coefficients were calculated using Spearman's rank correlation.

Results are shown as means with 95% confidence index (CI) or as median values with interquartile range (IQR) when appropriate. Differences were considered significant when $p < 0.05$.

The study protocol, adherent to Declaration of Helsinki, was approved by the Medical University of Silesia Bioethics Committee (KNW/0022/KB1/56/I/10) and all patients gave their written informed consent for participation in the study.

RESULTS

From the group of 71 enrolled patients, 65 (38 males, 27 females; mean age 53.6 (50.0-57.1) years) completed the study. Among 6 patients who were ruled out of the study 2 people died, 2 patients discontinued the study because of permanent decrease of serum PTH concentration below 150 pg/ml, one patient refused to continue the study due to paresthesia and one patient withdrew the consent for the study.

The mean daily dose of cinacalcet after 3 months of treatment was 41 (37-45) mg, the target serum PTH concentration was reached in 16 of 65 patients (24.6%). The dosing of intestinal phosphate binders and active vitamin D_3 analogues was flexible in order to avoid cinacalcet-related hypocalcemia and hypophosphatemia. A slight, but significant increase in the dosage of calcium carbonate, but no difference in the mean daily dose of alfacalcidol was observed (tab. 1).

In patients who completed the study, cinacalcet treatment caused a significant ($p < 0.0001$) decrease of serum PTH concentration – from 1089 (891-1286) pg/ml to 775 (574-976) pg/ml. There were no significant differences in the mean serum calcium ($p = 0.31$) and phosphate ($p = 0.09$) concentration during cinacalcet treatment (tab. 1).

During the treatment period the plasma leptin and serum CRP concentrations, body mass and body mass index (BMI) were stable (fig. 1, tab. 1).

In the correlation analyses a significant positive correlation was found between the plasma leptin concentration and BMI at the baseline and also after 3 month of treatment: $r = 0.49$; $p = 0.0004$ and $r = 0.47$; $p = 0.002$, respectively.

There were no significant correlations between the changes of leptin concentration and neither dose of cinacalcet ($r = 0.05$; $p = 0.27$), nor the decrease of serum PTH concentration ($r = -0.17$; $p = 0.13$).

Tab. 1. Serum concentration of PTH, calcium, phosphate; BMI and doses of alfacalcidol and calcium carbonate before and after 3 months of treatment with cinacalcet

	At the baseline	After 3 months of treatment	*p*
Serum PTH concentration (pg/ml)	1089 (891-1286)	775 (574-976)	< 0.0001
Serum CRP concentration (mg/l)	10.75 (8.97-12.53)	11.20 (9.26-13.16)	0.80
Serum calcium concentration (mmol/l)	2.14 (2.07-2.21)	2.10 (2.04-2.16)	0.31
Serum phosphate concentration (mmol/l)	2.09 (1.93-2.43)	1.99 (1.83-2.24)	0.09
BMI (kg/m^2)	26.6 (25.3-27.9)	26.5 (25.2-27.8)	0.21
Alfacalcidol dose (g/24h)	0.28 (0.18-0.39)	0.34 (0.21-0.46)	0.17
Number of patients treated with alfacalcidol	32 (49%)	36 (55%)	0.59
Calcium carbonate dose (g/24h)	3.52 (2.77-4.28)	3.91 (3.08-4.75)	0.02
Number of patients treated with calcium carbonate	58 (89%)	60 (92%)	0.76

PTH – parathormone; CRP – C-reactive protein; BMI – body mass index

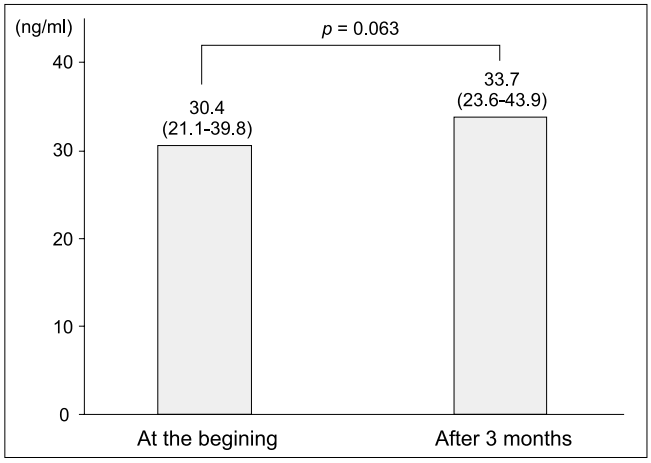

Fig. 1. Plasma concentration of leptin before and after 3 months of treatment with cinacalcet

DISCUSSION

In the current clinical study we have found that 3 months of treatment with cinacalcet in hemodialysed ESKD patients with sHPT did not influence plasma leptin concentration (fig. 1). The serum CRP concentration, as well as the body mass and body mass index of the enrolled patients also remained stable during the course of the study.

These results are in agreement with the only clinical study, conducted so far regarding the influence

of calcimimetics on plasma leptin concentration (21). In this study Hryszko et al. found no differences in leptinemia after 6-months treatment with cinacalcet. Taking into consideration the fact that nowadays leptin is considered to be a merely a marker of nutrition, and the fact that the BMI of enrolled patients remained stable, the above mentioned results could be expected.

On the other hand, Testerink et al. (22) found a decrease of plasma leptin concentration after alfacalcidol treatment in rats. Nevertheless, it is not likely that the increase in the dose of alfacalcidol may have influenced leptinemia in our study as the increase of alfacalcidol dose was not significant ($p = 0.17$). What is more, the study by Testerink et al. cannot be even remotely compared with the population of ESKD patients as it does not reflect the metabolic status of our patients. The rats in the abovementioned study had supraphysiological concentrations of serum vitamin D, while patients with ESKD are usually characterized by low vitamin D concentrations. Finally, the decrease of plasma leptin concentration in their study was most likely secondary to the animals' weight loss, while in our group of patients the BMI was constant during the entire observation period.

Our study has however some limitations. Definitely the most important is the lack of placebo controlled group. Still, as cinacalcet is nowadays commonly used in the treatment of sHPT, conducting a placebo-controlled study with this agent may rise some significant ethical issues. Another drawback might be the lack of more precise marker of the amount of adipose tissue than the BMI.

CONCLUSIONS

In summary, we have found that in hemodialysis patients with ESKD and sHPT three months of treatment with cinacalcet did not change significantly plasma leptin concentration.

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