ORIGINAL ARTICLE

Effect of secondary hyperparathyroidism treatment with cinacalcet on selected adipokines and markers of endothelial injury in hemodialysis patients: a preliminary report

Tomasz Hryszko, Szymon Brzosko, Alicja Rydzewska-Rosołowska, Ewa Koc-Żórawska, Beata Naumnik, Michał Myśliwiec

Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Białystok, Poland

KEY WORDS

adiponectin, cinacalcet, E-selectin, leptin, thrombomodulin

ABSTRACT

INTRODUCTION Disturbances in endothelial function, adipokines, and mineral metabolism due to secondary hyperparathyroidism (SHPT) shorten the lifespan in hemodialysis (HD) patients.

OBJECTIVES The aim of the study was to evaluate the effect of SHPT treatment with cinacalcet on selected adipokines and markers of endothelial injury in HD patients.

PATIENTS AND METHODS Soluble thrombomodulin (sTM), E-selectin, leptin, and adiponectin levels were measured in patients with SHPT at baseline and at 6 months of cinacalcet treatment.

RESULTS A total of 18 patients completed the study. SHPT treatment with cinacalcet decreased calcium, phosphate, and intact parathormone (iPTH) levels; however, no significant changes in sTM, E-selectin, leptin, or adiponectin were observed. iPTH levels after treatment correlated with age ($r = –0.51$, $P = 0.031$), mean cinacalcet dose ($r = 0.65$, $P = 0.004$), as well as baseline calcium ($r = 0.65$ $P = 0.003$), iPTH ($r = 0.59$, $P = 0.01$), E-selectin ($r = 0.56$, $P = 0.016$), and leptin ($r = –0.49$, $P = 0.039$).

CONCLUSIONS Cinacalcet treatment does not affect the markers of endothelial function and selected adipokines. Effectiveness of treatment may be modulated by E-selectin and leptin.

INTRODUCTION The population of patients on hemodialysis (HD) is being decimated by cardiovascular disease (CVD). The epidemic is caused by traditional risk factors for CVD as well as by those specific for HD population such as oxidative stress, abnormal adipokine levels, and secondary hyperparathyroidism (SHPT). The latter are thought to precipitate and propagate changes in the vascular bed including calcification,[1] atherosclerotic lesions,[2] and impaired vascular reactivity.[3] Moreover, recent years have provided evidence on close links between bone metabolism and adipokines[4] as well as between adipokines and the endothelium.[5,6]

Perception of ambient calcium by the cells is possible due to the presence of the calcium-sensing receptor (CSR). It is present in the organs involved in calcium homeostasis including the parathyroid glands,[7] intestine,[8] bone,[9] and kidney.[10] Interestingly, CSR was also found in tissues that are not involved in maintaining calcium homeostasis such as the brain,[11] endothelial cells,[12] adipocytes,[13] and aortic vascular smooth muscle cells.[14] It is postulated that CSR regulates such processes as blood pressure,[12] vascular calcification,[15] lipid metabolism,[16] and adipokine secretion.[17] Of note, a clinical study confirmed the role of CSR polymorphism in coronary heart disease as well as in cardiovascular and all-cause mortality.[18]

Cinacalcet, a positive allosteric modulator of CSR, increases sensitivity of CSR to extracellular calcium in the parathyroid glands and thus decreases parathormone (PTH) secretion. Cinacalcet has been approved for the treatment of SHPT in dialysis patients and is becoming an alternative to parathyroidectomy, although there is still no evidence that the use of cinacalcet in

Correspondence to:
Tomasz Hryszko, MD, Klinika Nefrologii i Transplantologii z Ośrodkiem Dializ, ul. Żurawia 14, 15-540 Białystok, Poland, phone/fax: +48-85-743-45-86, e-mail: tomhry@mp.pl
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the treatment of disturbed calcium-phosphate homeostasis translates into decreased CVD morbidity or mortality. Cinacalcet was shown to prevent the progression of aortic calcification and atherosclerosis in the animal model.[15,19] Also in vitro model suggested inhibitory effect of cinacalcet on lipolysis in adipocytes.[20] To our knowledge, the effect of SHPT treatment with cinacalcet on the markers of endothelial function or adipokines in HD patients has not been studied so far.

We examined the hypothesis that treatment of SHPT with cinacalcet affects endothelial function directly through CSR or indirectly by lowering intact PTH (iPTH) levels to the recommended values. We also sought to examine possible alterations in the levels of selected adipokines during treatment with the calcimimetic and a possible modulatory effect of these levels on the effectiveness of SHPT treatment. To minimize the potential confounding effect of vitamin D analogs or phosphate-binder therapy on the examined parameters, no changes in the above medications were allowed during the study.

PATIENTS AND METHODS

Study design This was a post hoc analysis of a 6-month, prospective, open-label trial.[21] The trial was designed to assess the effect of cinacalcet on the markers of bone metabolism in patients on chronic HD based on the study by Block et al.[22] The study protocol was described in detail elsewhere.[21] Briefly, adult subjects enrolled in the study were cinacalcet-naive, were in stable medical condition, had elevated iPTH levels above 44 pmol/l, and underwent HD 3 times a week. The dose of phosphate binders or vitamin D analogs within the preceding 30 days and during the study was not changed. The initial dose of cinacalcet (Mimpara, Amgen) was 30 mg orally once daily at bedtime. Every 3 to 4 weeks, the doses were titrated up to 180 mg once daily if iPTH levels were above 33 pmol/l and serum calcium levels were at least 1.95 mmol/l. The dose was not increased in the case of symptomatic hypocalcemia, serum calcium levels below 1.95 mmol/l, or an adverse event that precluded dose escalation. The dose was reduced if PTH levels were below 16.5 pmol/l or if an adverse event required dose reduction. Patients were withdrawn from the study and excluded from the analysis if treatment with a phosphate binder or vitamin D analog was started or their dose was changed. Compliance was monitored indirectly. Subjects were asked to return the packaging of the drug on the day when the laboratory parameters were evaluated and the remaining pills were counted.

All patients provided written informed consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki and the research protocol was reviewed and accepted by the local ethics committee.

Measurements and assays Venous blood (plasma and serum) was collected at baseline and at 6 months in the morning on a day after dialysis session, after an overnight fast and at least 12 hours after the last dose of cinacalcet. Blood after centrifugation was aliquoted and frozen until assayed. Calcium, phosphate, albumin, hemoglobin, white blood cells and platelets were measured using standard methods. iPTH was measured with an electrochemiluminescence immunoassay (IMMULITE Siemens Medical Solutions Diagnostics, Erlangen, Germany). Soluble thrombomodulin (sTM, endothelial injury marker), E-selectin (marker of endothelial activation), and selected adipokines such as adiponectin and leptin were measured using a commercially available enzyme-linked immunosorbent assay (Quantikine, R&D Systems, Abingdon, United Kingdom).

Statistics Data are presented as a mean ± standard deviation or median (range) as appropriate. The distribution was tested with the Shapiro-Wilk's *W* test. Skewed variables were transformed using natural logarithm to achieve Gaussian distribution (E-selectin, iPTH, leptin). Paired *t* test or sign test was used to evaluate the changes from baseline. Associations between the variables were examined with the Pearson or Spearman test depending on whether the assumptions were met. A two-tailed $P < 0.05$ was considered significant. All analyses were performed with Statistica 8.0 for Windows (StatSoft Inc., Tulsa, Oklahoma, United States).

RESULTS

Study population Of 34 recruited patients, 18 completed the study. The reasons for early discontinuation are presented in the TABLE. The mean age of patients was 64.9 ±13.0 years. There were 12 women (67%). Cardiovascular disease was confirmed in 10 patients (56%); 4 patients (22%) had diabetes. Patients underwent HD for median 27.1 months (min–max value, 2.1–99.6), 3 times a week and their mean urea reduction rate was 67.4% ±7.7%. The mean hemoglobin value in study subjects was 107 ±15 g/l and they received the mean of 6722.2 ±3139 I.U. per week of an erythropoiesis-stimulating agent.

Compliance during the study was above 95%. All 18 patients (100%) received calcium carbonate and 5 (28%) – vitamin D analog (Alfadiol, GlaxoSmithKline Pharmaceutical SA, Poland) in constant doses. The mean cinacalcet dose at 6 months was 65 ±36 mg per day.

TABLE Reasons for discontinuing participation in the study

Reason	n (%)
alteration in the dose of vitamin D or phosphate binder	10 (29)
kidney transplantation	2 (6)
death	1 (3)
consent withdrawal	1 (3)
stroke	1 (3)
nausea	1 (3)

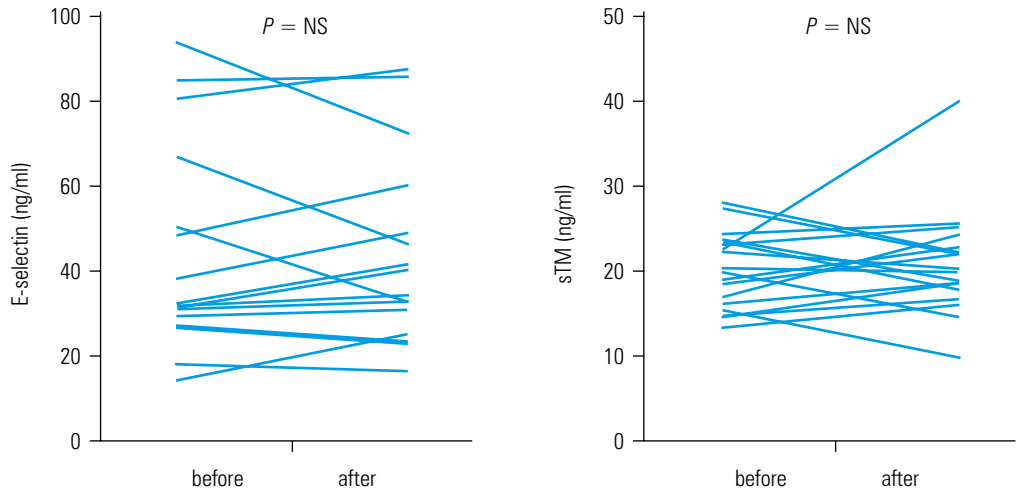

FIGURE 1 E-selectin and soluble thrombomodulin (sTM) levels at baseline and at 6 months of treatment with cinacalcet (raw data before logarithmic transformation are presented)
Abbreviations: NS – nonsignificant

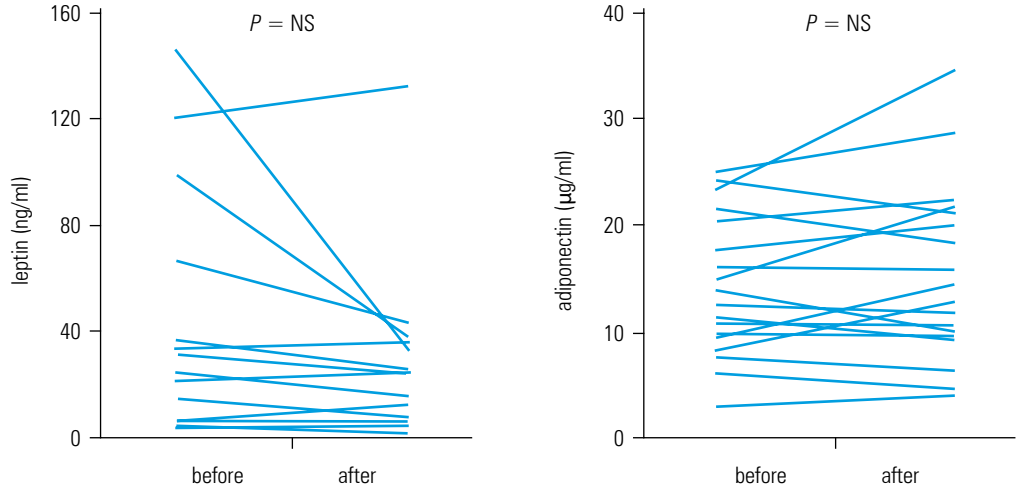

FIGURE 2 Leptin and adiponectin levels at baseline and at 6 months of treatment with cinacalcet (raw data before logarithmic transformation are presented)
Abbreviations: see FIGURE 1

Biochemical measures After a 6-month treatment with cinacalcet, baseline serum iPTH levels decreased from 102.9 (45.7–275.0) pmol/l to 53.6 (10.8–275.0) pmol/l (P = 0.001). We also observed nonsignificant declines in serum calcium levels from 2.5 ±0.4 mmol/l to 2.4 ±0.3 mmol/l (P = 0.35) and phosphate levels from 1.9 ±0.3 mmol/l to 1.7 ±0.5 mmol/l (P = 0.29). There were no significant changes in E-selectin (log E-sel, 3.62 ±0.52 vs. 3.65 ±0.46 ng/ml, P = 0.73) or sTM levels (20.12; 13.34–28.03 vs. 20.03; 9.87–39.98 ng/ml, P = 0.81) (FIGURE 1). Moreover, there were no significant differences in the levels of adiponectin (14.19 ±6.60 vs. 15.28 ±8.24 µg/ml, P = 0.24) or leptin (log leptin, 9.75 ±1.31 vs. 9.55 ±1.15 ng/ml, P = 0.15) (FIGURE 2).

Correlations between the assessed parameters and intact parathormone levels after cinacalcet treatment iPTH levels at 6 months of treatment with cinacalcet correlated significantly with age (r = –0.51, P = 0.031), mean cinacalcet dose (r = 0.65, P = 0.004), and baseline levels of calcium (r = 0.65, P = 0.003), iPTH (r = 0.59, P = 0.01), E-selectin (r = 0.56, P = 0.016), leptin (r = –0.49, P = 0.039). but not with dialysis vintage (r = –0.09, P = 0.76), sTM (r = 0.09, P = 0.74), adiponectin (r = –0.28, P = 0.26), hemoglobin (r = –0.32, P = 0.22), phosphate (r = 0.14, P = 0.59), and albumin (r = 0.08, P = 0.74).

DISCUSSION

The aim of the study was to evaluate the effect of SHPT treatment with cinacalcet on the markers of endothelial function in HD patients. There were no significant changes in the evaluated markers of endothelial function despite a significant decrease in iPTH levels. While interpreting the results, it is not possible to separate direct (through CSR) from indirect systemic (improvement of mineral homeostasis) effects of cinacalcet. Therefore, both actions must be considered together. Although in vitro [23] and animal studies[15,19] provided data on the beneficial effect of CSR stimulation in the context of vascular changes, results from clinical studies are inconclusive. Both beneficial[24,25] and neutral[26,27] cardiovascular effects of treatment with cinacalcet have been described. Our results may be also supported indirectly by the reported neutral effects of parathyroidectomy on the markers of endothelial activation and injury in patients with primary hyperparathyroidism.[28] The above discrepancy may result from the fact that patients with end-stage renal disease have reduced arterial

CSR expression,[29] and this decrease might be present to a varying extent among subjects. Moreover, CSR polymorphism is responsible for the development of cardiovascular complications.[18] Thus, the vascular actions of cinacalcet appear to be complex and the overall effect probably depends on numerous factors. While interpreting the current results, it must be acknowledged that only 2 markers of endothelial function were evaluated and that small sample size made it difficult to draw firm conclusions.

There is growing evidence on the link between bone metabolism and the adipose tissue in the general population and in patients with end-stage renal disease.[30] Moreover, in vitro results confirming the presence of CSR in the adipose tissue,[13] antilipolytic effect of cinacalcet,[20] and the potential regulatory role of extracellular calcium ions in adipocyte metabolism[16,17] provided the rationale for investigating the effect of treatment with calcimimetic on selected adipokines. The study did not show any influence of SHPT treatment with cinacalcet on leptin or adiponectin levels. To our knowledge, there is no data concerning the above issue in HD patients with SHPT, and the data are unequivocal in the population of patients with primary hyperparathyroidism. Delfini et al.[31] reported elevated levels of leptin and decreased levels of adiponectin in patients with metabolic syndrome and put forward a hypothesis about the possible involvement of the above disturbances in the development of cardiovascular complications. On the other hand, a study by Bollerslev et al.[28] did not confirm the previous findings and failed to show any effect of parathyroidectomy on those adipokines, which is in agreement with our findings.

Effectiveness of SHPT treatment with cinacalcet has been proved in many clinical studies.[22,32] Unfortunately, not all patients treated with a calcimimetic achieve a desirable reduction in iPTH levels. To date, little is known about the factors predicting responsiveness to treatment.

In a univariate model, baseline calcium and iPTH levels correlated with post-treatment iPTH concentration. It is probably a hallmark of SHPT severity, as in tertiary hyperparathyroidism when hypercalcemia is present and the likelihood of conservative management success is low. The association between baseline iPTH levels and worse effects of therapy is in line with the previous reports.[22,32]

To our knowledge, for the first time an inverse relation between baseline leptin levels and the effectiveness of treatment has been observed. It is postulated that adipokines are associated with bone metabolism.[30] Zoccali et al.[33] observed a negative correlation between leptin and iPTH levels in HD male patients.[33] On the other hand, Kokot et al.[34] did not find a similar association but speculated on the possible feedback loop between leptin and iPTH. Our results do not confirm the above hypothesis because there were no significant changes in leptin or adiponectin levels during treatment with cinacalcet despite a significant decrease in iPTH levels. Our findings are supported by the results of Bollerslev et al.[28] who did not show any beneficial effects of parathyroidectomy on the level of the above adipokines. It appears that the relation between adipokines and bone metabolism is complex and multivariate.

The association between soluble E-selectin and the effectiveness of SHPT treatment with cinacalcet is a conundrum. E-selectin, which is only expressed on the activated endothelial cells, is probably a mere indicator of advanced disturbances in mineral metabolism – a consequence of severe SHPT as suggested by Arici et al.[35] Thus, the efficacy of pharmacological treatment is limited.

The study has several limitations. Lack of the control arm and small sample size makes it difficult to draw definite conclusions about the effect of SHPT treatment with cinacalcet on the markers of endothelial function and selected adipokines. On the other hand, our results are strengthened by prospective study design and the fact that no modifications of drugs were allowed that could potentially affect mineral and bone metabolism (such as active vitamin D analogs or phosphate binders). Thus, the observed changes might be attributed to calcimimetic treatment, although data from a large clinical trial are needed to confirm our results.

In conclusion, cinacalcet treatment of SHPT in HD patients does not affect the levels of endothelial injury markers or selected adipokines. The baseline calcium and iPTH levels are associated with the effectiveness of treatment with a calcimimetic. Leptin and E-selectin levels may increase the effectiveness of SHTP treatment with cinacalcet in HD patients.

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Wpływ leczenia wtórnej nadczynności przytarczyc cynakalcetem u chorych hemodializowanych na wybrane adipokiny i wskaźniki uszkodzenia śródbłonka – badanie pilotażowe

Tomasz Hryszko, Szymon Brzosko, Alicja Rydzewska-Rosołowska, Ewa Koc-Żórawska, Beata Naumnik, Michał Myśliwiec

Klinika Nefrologii i Transplantologii z Ośrodkiem Dializ, Uniwersytet Medyczny w Białymstoku, Białystok

SŁOWA KLUCZOWE

adiponektyna, cynakalcet, leptyna, selektyna E, trombomodulina

STRESZCZENIE

WPROWADZENIE Zaburzenia funkcji śródbłonka, adipokin oraz gospodarki mineralnej w przebiegu wtórnej nadczynności przytarczyc (WNP) wpływają na skrócenie długości życia chorych hemodializowanych.

CELE Celem badania była ocena wpływu leczenia WNP cynakalcetem na wybrane adipokiny oraz wskaźniki uszkodzenia śródbłonka u chorych hemodializowanych.

PACJENCI I METODY Stężenie rozpuszczalnej frakcji trombomoduliny (*soluble thrombomodulin* – sTM), selektyny E, leptyny i adiponektyny zostały oznaczone przed rozpoczęciem leczenia i po 6 miesiącach leczenia WNP cynakalcetem.

WYNIKI Badanie ukończyło 18 pacjentów. W trakcie leczenia WNP cynakalcetem obserwowano zmniejszenie stężenia wapnia, fosforanów oraz *intact* parathormonu (iPTH), nie obserwowano natomiast istotnych zmian stężenia sTM, selektyny E, leptyny i adiponektyny. Stężenie iPTH po leczeniu korelowało z wiekiem ($R = –0,51$; $p = 0,031$), średnią dawką cynakalcetu ($R = 0,65$; $p = 0,004$), stężeniem wapnia przed leczeniem ($R = 0,65$; $p = 0,003$), wyjściowym stężeniem iPTH ($R = 0,59$; $p = 0,01$) oraz z wyjściowym stężeniem selektyny E ($R = 0,56$; $p = 0,016$) i leptyny ($R = –0,49$; $p = 0,039$).

WNIOSKI Leczenie WNP cynakalcetem nie wpływa na markery funkcji śródbłonka oraz wybrane adipokiny. Skuteczność leczenia może być modulowana przez selektynę E i leptynę.

Adres do korespondencji:
lek. Tomasz Hryszko, Klinika Nefrologii i Transplantologii z Ośrodkiem Dializ, ul. Żurawia 14, 15-540 Białystok, tel./fax: 85-743-45-86, e-mail: tomhry@mp.pl

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