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Vitamin D deficiency in obesity and its relationship to insulin resistance and plasma leptin levels – preliminary study**

Niedobory witaminy D u osób otyłych i ich związek z insulinoopornością oraz leptyną – doniesienie wstępne

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Słowa kluczowe

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Summary

Introduction. Obesity is a risk factor for vitamin D deficiency and there is some evidence that vitamin D may be involved in the pathogenesis of insulin resistance.

Aim. The aim of the study was to evaluate whether vitamin D deficiency is associated with insulin resistance and leptin level in obese subjects.

Material and methods. 43 obese (body mass index (BMI) ≥ 35 kg/m^2) individuals before bariatric surgery and 16 healthy volunteers with normal body weight were enrolled in this study. In all subjects serum level of glucose, 25-hydroxyvitamin D (25(OH)D), calcium, insulin, leptin, leptin soluble receptor were evaluated, insulin resistance was estimated by the homeostasis model assessment (HOMA-IR), free leptin index was calculated.

Results. In the obese group 90% of patients had lower than recommended level of 25(OH)D, in the control group – 75%. In all investigated groups significant negative correlations between 25(OH)D and insulin, HOMA-IR, leptin, and free leptin index were found but in obese subjects this correlations were not observed. There were significant negative correlations between serum calcium and BMI, insulin, HOMA-IR, leptin, and free leptin index and a significant positive correlation between serum calcium and leptin receptor in all investigated groups. In obese subjects there were correlations between calcium levels and soluble leptin receptor as well as free leptin index.

Conclusions. Vitamin D deficiency and insufficiency are common in obese and normal weight subjects. There is a lack of correlation between 25(OH)D concentration and insulin resistance parameters and leptin in obese subjects. Vitamin D may impact leptin activity through calcium concentration.

Streszczenie

Wstęp. Otyłość jest czynnikiem ryzyka niedoboru witaminy D. Istnieją dowody, że witamina D może odgrywać rolę w patogenezie insulinooporności.

Cel pracy. Celem pracy była ocena, czy u osób otyłych niedobór witaminy D jest związany z insulinoopornością oraz stężeniem leptyny.

Materiał i metody. Do badania włączono 43 otyłych (wskaźnik masy ciała (BMI) ≥ 35 kg/m^2) pacjentów przed operacją bariatryczną oraz 16 zdrowych ochotników z prawidłową masą ciała. U wszystkich oszacowano w surowicy stężenie: 25-hydroksywitaminy D (25(OH)D), wapnia, glukozy, insuliny, leptyny, rozpuszczalnego receptora leptyny, dokonano oceny insulinooporności przy pomocy modelu homeostatycznego (HOMA-IR) oraz obliczono indeks wolnej leptyny.

Wyniki. W grupie otyłych 90% osób miało niższe niż zalecane stężenie 25(OH)D, w grupie kontrolnej – 75%. W całej grupie stwierdzono istotną ujemną korelację między 25(OH)D

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a insuliną, HOMA-IR, leptyną i indeksem wolnej leptyny, natomiast w grupie otyłych powyższe korelacje nie były obserwowane. Stwierdzono istotną ujemną korelację między stężeniem wapnia a BMI, insuliną, HOMA-IR, leptyną oraz indeksem wolnej leptyny, a także istotną dodatnią korelację między stężeniem wapnia a stężeniem wolnego receptora leptyny w całej badanej grupie. W grupie otyłych zaobserwowano korelację między stężeniem wapnia a stężeniem rozpuszczalnego receptora leptyny i indeksem wolnej leptyny.

Wnioski. Niedobór i deficyt witaminy D są częste zarówno u osób otyłych, jak i z prawidłową masą ciała. U osób otyłych nie stwierdza się korelacji między stężeniem 25(OH)D a parametrami insulinooporności oraz leptyną. Witamina D może wpływać na aktywność leptyny poprzez wpływ na stężenie wapnia.

INTRODUCTION

Health care of obese people is one of the biggest challenges of medicine nowadays. The new IASO/IOTF (International Association for the Study of Obesity/International Obesity Task Force) analysis (2010) estimates that approximately 1.0 billion adults worldwide are currently overweight (with body mass index (BMI) 25-29.9 kg/m^2), and another 475 million are obese (1) which means that around 1.5 billion adults have inappropriate, elevated body mass. The survey performed in Poland in the years 2003-2007 found that among men 40.3 percent (aged 20+) were overweight and 20.8 percent (aged 20+) were obese. Among females 28.4 percent (aged 20+) were overweight and 23.8 percent (aged 20+) were obese (2).

Obesity is the major determinant of metabolic syndrome, presumably through its effect on insulin resistance. Insulin resistance is the condition in which normal amounts of insulin are inadequate to cause a proper insulin response from fat, muscle and liver cells. Each standard deviation (SD) increase in visceral adipose tissue mass increases the odds of insulin resistance by 80% (3).

The mechanisms of insulin resistance are not elucidated yet in details. In the first hypothesis, lipid accumulation in skeletal muscle and liver cells plays the central role, however in the second theory, the most important mechanism is lipid accumulation in adipocytes and local inflammation. There is also some evidence that vitamin D may be involved in the pathogenesis of insulin resistance (4). This observation is especially important in obesity because in obese subjects aberrations in the correlation between the vitamin D and endocrine system were identified (5). Many studies reported an association between obesity and low serum 25-hydroksyvitamin D (25(OH)D) concentrations, as well as with high concentrations of parathyroid hormone (PTH) (6, 7).

Vitamin D is a regulator of bone and mineral metabolism homeostasis. In addition to its classical actions, vitamin D plays multiple biological roles. In details, more than 200 genes are controlled directly or indirectly by the active form of this vitamin – 1,25 dihydroxyvitamin D (1,25(OH)$_2$D), regulating cellular proliferation, differentiation, apoptosis and angiogenesis (8). Moreover, vitamin D receptor (VDR) is distributed in more than 38 types of tissue (9) including insulin-responsive tissues and pancreatic beta cells.

Epidemiological studies showed correlations between low serum 25(OH)D concentration, an indicator of organism supply with vitamin D, and increased insulin resistance (10, 11). Vitamin D may have effect on insulin resistance through direct action via VDR or indirectly via calcium and PTH levels. 1,25(OH)$_2$D can bind to VDR in beta cells and therefore may stimulate the expression of insulin receptor and promote insulin-mediated glucose transport (12). Additionally, vitamin D may reduce the low-grade chronic inflammation that is present in obesity by decreasing the production of inflammatory factors (i.e. cytokines) by activated macrophages (13).

It is widely known that vitamin D regulates serum calcium levels. Calcium is a crucial ion in insulin action (14), thus vitamin D deficiency may induce hypocalcaemia and insulin resistance at the target tissues level. On the other hand, hypovitaminosis D induces the elevation of PTH concentration. Some studies demonstrated that PTH decreased insulin-induced glucose transport in adipocytes (15). It has been also reported that PTH in obese adolescents was associated with biomarkers of insulin resistance and inflammation, independently of vitamin D levels (16).

Interestingly, vitamin D may impact on adipocytokines homeostasis. 25(OH)D levels were positively correlated with adiponectin (17), which increases insulin sensitivity and reveals anti-inflammatory action. However, data concerning the correlation between leptin, an adipokine that plays a key role in regulating energy intake and energy expenditure in human, and vitamin D are controversial. Some studies reported that 1,25(OH)$_2$D suppressed leptin (18) while other authors demonstrated that 1,25(OH)$_2$D stimulated leptin production in mouse adipose tissue (19).

The role of Vitamin D in the development of insulin resistance is well supported by experimental data, however results from interventional studies provided contradictory results. Some studies (20) failed to confirm effects on insulin sensitivity after supplementation with vitamin D, while in others, this kind of improvement was observed (21). Recently published misanalysis demonstrated, that currently there is an insufficient evidence of beneficial effect to recommend vitamin D supplementation as a means of improving glycaemia or lowering insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance (22).

AIM

Because of these ambiguous data, we aimed to evaluate whether vitamin D deficiency is associated with insulin resistance and leptin level in obese subjects.

MATERIAL AND METHODS

Subjects

Forty three obese individuals with body mass index (BMI) ≥ 35 kg/m^2, including 12 male and 31 females, were enrolled in the study. All individuals were Caucasians and were recruited among the patients of Department of Family, Internal Medicine and Metabolic Bone Diseases, Orlowski Hospital, Centre of Postgraduate Medical Education in Warsaw, Poland. All subjects were admitted to the hospital for internal examination prior to the bariatric surgery. Exclusion criteria from the study were as follows: selected endocrine dysfunctions (hyper- or hypothyreosis, Cushing disease) chronic kidney and liver disease. None of examined subjects had a history of excessive alcohol consumption. None of subjects took vitamin D supplements. The control group consisted of 16 healthy volunteers (6 male and 10 female) with normal body weight (BMI 19-24 kg/m^2).

The study protocol was accepted by the Bioethical Committee of the Centre of Postgraduate Medical Education.

Blood analyses

Blood samples were obtained at 8.00 am after overnight fasting and were immediately centrifuged at 4°C. Plasma was stored at -30°C for further analyses of insulin, leptin and leptin soluble receptor concentration. Additionally serum was immediately used for other analytical analyses.

Insulin concentration was measured using IRMA methods (Immunotech, Czech Republic). Leptin level was estimated with RIA method (Linco Research). Leptin soluble receptor concentration was assessed with ELISA (Bio Vendor Laboratory Medicine).

Intra- and inter-assay coefficient was below 10% for all investigated parameters. Leptin, leptin soluble receptor and insulin levels were investigated in the Department of Neuroendocrinology, Centre of Postgraduate Medical Education in Warsaw.

Blood glucose and calcium concentrations were measured by certified hospital laboratory applying standard clinical biochemistry methods. 25(OH)D concentration was measured by the same laboratory using ARCHITECT 25-OH Vitamin D assay (fully automated immunoassay).

In all subjects insulin resistance was estimated by homeostasis model assessment (HOMA-IR), according to the formula:

HOMA-IR = fasting glucose (mmol/l) x fasting plasma insulin (μIU/ml) / 22.5.

Free leptin index (FLI) was calculated as a quotient leptin / leptin receptor X 100.

Statistical analysis

Statistica 6.1 was used for statistical analysis. Data are shown as means ± standard deviation. The normality of distribution was investigated using the Shapiro-Wilk test. The differences between groups were calculated using Mann-Whitney U-test. The Spearman test was used to estimate correlations between 25(OH)D and biochemical parameters as well as serum calcium concentrations and BMI and adipokines. Significance level was defined as p-value < 0.05.

RESULTS

Data concerning clinical and biochemical parameters are presented in table 1.

Table 1. Data of the study and control groups.

Parameter	Obese (n = 43)	Control (n = 16)	P
Age (years)	40.09 ± 10.77	33.93 ± 6.86	< 0.05
BMI (kg/m^2)	43.7 ± 6.48	21.87 ± 2.04	< 0.001
Fasting blood glucose (mg/dl)	104.51 ± 26.0	82.0 ± 8.77	< 0.001
Fasting insulin (μUI/ml)	21.64 ± 13.18	8.31 ± 0.30	< 0.001
HOMA-IR	5.60 ± 3.74	1.64 ± 0.51	< 0.001
25(OH)D (ng/ml)	20.62 ± 5.94	24.86 ± 8.32	= 0.055
Serum calcium concentration (mg/dl)	8.88 ± 1.06	9.33 ± 0.24	< 0.001
Leptin (ng/ml)	38.44 ± 12.12	9.47 ± 0.51	< 0.001
Leptin receptor (ng/ml)	10.37 ± 5.16	18.74 ± 4.18	< 0.001
Free leptin index	445.45 ± 225.74	47.82 ± 28.68	< 0.001

BMI – body mass index; HOMA-IR – homeostasis model assessment of insulin resistance; 25(OH)D – 25-hydroxyvitamin D; P – p-value
Conversion factors for SI units:
glucose (mg/dl) x 0.055 = glucose (mmol/l)
insulin (UI/ml) x 6 = insulin (pmol/l)
calcium (mg/dl) x 0.25 = calcium (mmol/l)
25(OH)D (ng/ml) x 2.496 = 25(OH)D (nmol/l)

We found significant differences when comparing the following parameters found in obese and control subjects: age, BMI, fasting glucose levels, HOMA-IR, leptin, leptin receptor, free leptin index and serum calcium concentration. Obese subjects had lower 25(OH)D level but this difference was not significant. In the obese group 90% of patients had lower than recommended level of 25(OH)D (< 30 ng/ml) while in the control group only 75%. In the obese group 41% individuals had suboptimal status of vitamin D (20-30 ng/ml) and 48% of them were vitamin D deficient. In the control group 50% of subjects had suboptimal status of vitamin D and 25% of them were vitamin D deficient.

In all investigated groups we found significant negative correlations between 25(OH)D and insulin, HOMA-IR, leptin, and free leptin index (tab. 2).

In obese subjects there were no significant correlations between 25(OH)D and investigated parameters.

We observed also significant negative correlations between serum calcium and BMI, insulin, HOMA-IR, leptin, and free leptin index and significant positive correlation between serum calcium and leptin receptor in all investigated groups (tab. 3).

Table 2. Correlations between 25(OH)D and biochemical parameters in all investigated groups.

Parameter A	Parameter B	R	P
25(OH)D	Insulin	-0.35	< 0.01
25(OH)D	HOMA-IR	-0.30	< 0.05
25(OH)D	Leptin	-0.30	< 0.05
25(OH)D	Leptin receptor	0.23	= 0.07
25(OH)D	Free leptin index	-0.32	< 0.05

25(OH)D – 25-hydroxyvitamin D; HOMA-IR – homeostasis model assessment of insulin resistance; R – Spearman's correlation coefficient; P – p-value

Table 3. Correlations between serum calcium concentrations and biochemical parameters in all participants of the study.

Parameter A	Parameter B	R	P
Serum calcium concentration	BMI	-0.43	< 0.001
Serum calcium concentration	Insulin	-0.37	< 0.01
Serum calcium concentration	HOMA-IR	-0.29	< 0.05
Serum calcium concentration	Leptin	-0.51	< 0.001
Serum calcium concentration	Leptin receptor	0.55	< 0.001
Serum calcium concentration	Free leptin index	-0.54	< 0.001

BMI – body mass index; HOMA-IR – homeostasis model assessment of insulin resistance; R – Spearman's correlation coefficient; P – p-value

In obese subjects there were correlations only between calcium levels and soluble leptin receptor as well as free leptin index (tab. 4).

Table 4. Correlations between serum calcium concentrations and biochemical parameters in obese patients.

Parameter A	Parameter B	R	P
Serum calcium concentration	Leptin receptor	0.34	< 0.05
Serum calcium concentration	Free leptin index	-0.30	< 0.05

R – Spearman's correlation coefficient; P – p-value

DISCUSSION

In this study we analyzed the association of vitamin D levels with insulin resistance and leptin level in obese subjects. Serum levels of 25(OH)D, which is a marker for vitamin D status, had a tendency to lower values in obese patients than in controls, but the difference was not statistically significant. Normal range of vitamin D levels are above 30 ng/ml (23). In our study mean serum level of 25(OH)D was 20.62 ng/ml in obese subjects and 24.86 ng/ml in normal weight subjects. In the obese group 90% of patients had lower than recommended level of 25(OH)D and in the control group – 75%. This observation is not surprising, because vitamin D deficiency and insufficiency are common in the world (24).

We found significant negative correlations between 25(OH)D and insulin, HOMA-IR in all investigated group, but these correlations were not present in obese subjects. In the study of Roth et al (25),the authors assessed vitamin D deficiency in obese children and its relationship to insulin resistance and found that 25(OH)D shoved a negative correlation with HOMA-IR in all (normal weight and obese) studied subjects. Moreover, in obese subjects there was a significant trend towards higher insulin concentrations and HOMA-IR in those individuals with lower 25(OH)D concentration. Conversely, Torun et al. (26) found that insulin resistance of the obese subjects, who were vitamin D deficient and insufficient did not differ from those with vitamin D sufficiency.

In our study there was a significant negative correlation between 25(OH)D, leptin and free leptin index in the whole group of subjects, but in the obese no correlation between these parameters was seen. Study of Vilarrasa et al. (27), investigating relation of plasma 25(OH)D to adipokines in both healthy and morbidly obese population, revealed that the correlation between 25(OH)D and leptin was observed in healthy subjects only.

Vitamin D is essential in bone mineralization and calcium homeostasis. The biologically active form of this vitamin,1,25$(OH)_2$D, is formed in the kidneys from 25(OH)D. 1,25$(OH)_2$D stimulates bone resorption and intestinal calcium absorption, leading to an increase in serum calcium concentration. Interestingly, obese subjects from our study, who had lower 25(OH)D concentration then normal weight subjects, had also lower serum calcium concentration. We observed significant negative correlations between serum calcium and BMI, insulin, HOMA-IR, leptin, and free leptin index and a significant positive correlation between serum calcium and soluble leptin receptor in all investigated groups. In obese subjects there were correlations between calcium and leptin receptor as well free leptin index only. These findings suggest that calcium may be an important bioactive component of some parameters of metabolic syndrome and it is possible that vitamin D does not directly influence insulin sensitivity but acts through calcium concentration. Calcium is a very important intracellular messenger and there is an evidence of link between extracellular calcium levels and free cytosolic calcium (28). In the experiment in which rodent adipocytes were incubated in the absence of calcium or in the presence of intracellular calcium chelators, glucose plus insulin failed to stimulate leptin secretion and these results indicated that acute leptin secretion was calcium dependent. On the contrary, basal leptin was secreted spontaneously and calcium independently (29). In other study performed on adipocytes isolated from rat white adipose tissue, it was shown that calcium is essential for the stimulatory effect of insulin on leptin secretion through its permissive role on glucose uptake (30). However, little is known about the regulatory function of calcium in relation with leptin secretion in humans. Insulin-resistant obese individuals have elevated plasma leptin levels, and it might be speculated that calcium insensitivity or calcium homeostasis disturbance contributes to increase leptin secretion. In blood leptin circulates as free and protein-bound forms. A soluble leptin receptor has been shown to account for the majority of the serum leptin

binding activity (31) and it plays a role in the regulation of the biological activity of leptin. There was a negative correlation between this receptor and the body mass index (32). To our knowledge, this is the first study that estimates relationship between human soluble leptin receptor concentrations and vitamin D and calcium in obese subjects.

CONCLUSIONS

In conclusion, vitamin D deficiency and insufficiency are commonly found in both obese and normal weight subjects. There is a lack of correlation between 25(OH)D concentration and insulin resistance parameters and leptin in obese subjects but in this particular population there is a correlation between calcium concentration and leptin receptor as well as free leptin index. This indicates that vitamin D may impact leptin activity through calcium concentration. Although calcium may play a role in leptin activity and insulin resistance, the full mechanism of its action still remains to be clearly elucidated, thus further investigations are needed.

BIBLIOGRAPHY

1. http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic.
2. http://www.iaso.org/resources/world-map-obesity.
3. McLaughlin T, Lamendola C, Liu A et al.: Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab 2011; 96: 1756-1760.
4. Chiu KC, Chu A, Go VL et al.: Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004; 79: 820-825.
5. Bell NH, Epstein S, Greene A et al.: Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest 1985; 76: 370-373.
6. Czerwińska E, Marcinowska-Suchowierska E, Walicka M et al.: The influence of bariatric surgery on calcium homeostasis and biochemical-markers of bone turnover in patients with morbid obesity. Endokrynol Pol 2007; 58: 130-138.
7. Parikh SJ, Edelman M, Uwaifo GI et al.: The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004, 89: 1196-1199.
8. Sung CC, Liao MT, Lu KC et al.: Role of vitamin D in insulin resistance. J Biomed Biotechnol 2012; 2012: 634195.
9. Haussler MR, Haussler CA, Bartik L et al.: Vitamin D receptor: molecular signaling and actions of nutritional ligands in disease prevention. Nutr Rev 2008; 66 (suppl. 2): S98-S112.
10. Scragg R, Sowers M, Bell C: Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004; 27: 2813-2818.
11. Danziger J, Biggs ML, Niemi M et al.: Circulating 25-hydroxyvitamin D is associated with insulin resistance cross-sectionally but not longitudinally in older adults: The Cardiovascular Health Study. Metabolism 2013; 62: 1788-1794.
12. Maestro B, Campión J, Dávila N et al.: Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J 2000; 47: 383-391.
13. Van Belle TL, Gysemans C, Mathieu C: Vitamin D and diabetes: the odd couple. Trends Endocrinol Metab 2013; 24: 561-568.
14. Hagström E, Hellman P, Lundgren E et al.: Serum calcium is independently associated with insulin sensitivity measured with euglycaemic-hyperinsulinaemic clamp in a community-based cohort. Diabetologia 2007; 50: 317-324.
15. Chang E, Donkin SS, Teegarden D: Parathyroid hormone suppresses insulin signaling in adipocytes. Mol Cell Endocrinol 2009; 307: 77-82.
16. Alemzadeh R, Kichler J: Parathyroid hormone is associated with biomarkers of insulin resistance and inflammation, independent of vitamin D status, in obese adolescents. Metab Syndr Relat Disord 2012; 10: 422-429.
17. Kardas F, Kendirci M, Kurtoglu S: Cardiometabolic risk factors related to vitamin d and adiponectin in obese children and adolescents. Int J Endocrinol 2013; 2013: 503270.
18. Menendez C, Lage M, Peino R et al.: Retinoic acid and vitamin D_3 powerfully inhibit in vitro leptin secretion by human adipose tissue. J Endocrinol 2001; 170: 425-431.
19. Kong J, Chen Y, Zhu G et al.: 1,25-Dihydroxyvitamin D_3 upregulates leptin expression in mouse adipose tissue. J Endocrinol 2013; 216: 265-271.
20. Tai K, Need AG, Horowitz M et al.: Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. Nutrition 2008; 24: 950-956.
21. Nazarian S, St Peter JV, Boston RC et al.: Vitamin D_3 supplementation improves insulin sensitivity in subjects with impaired fasting glucose. Transl Res 2011; 158: 276-281.
22. George PS, Pearson ER, Witham MD: Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabet Med 2012; 29: e142-e150.
23. Płudowski P, Karczmarewicz E, Bayer M et al.: Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 2013; 64: 319-327.
24. Wahl DA, Cooper C, Ebeling PR et al.: A global representation of vitamin D status in healthy populations. Arch Osteoporos 2012; 7: 155-172.
25. Roth CL, Elfers C, Kratz M et al.: Vitamin D deficiency in obese children and its relationship to insulin resistance and adipokines. J Obes 2011; 2011: 495101.
26. Torun E, Gönüllü E, Ozgen IT et al.: Vitamin d deficiency and insufficiency in obese children and adolescents and its relationship with insulin resistance. Int J Endocrinol 2013; 2013: 631845.
27. Vilarrasa N, Vendrell J, Maravall J et al.: Is plasma 25(OH)D related to adipokines, inflammatory cytokines and insulin resistance in both a healthy and morbidly obese population? Endocrine 2010; 38: 235-242.
28. Chow JY, Estrema C, Orneles T et al.: Calcium-sensing receptor modulates extracellular Ca (2+) entry via TRPC-encoded receptor-operated channels in human aortic smooth muscle cells. Am J Physiol Cell Physiol 2011; 301: C461-C468.
29. Levy JR, Gyarmati J, Lesko JM et al.: Dual regulation of leptin secretion: intracellular energy and calcium dependence of regulated pathway. Am J Physiol Endocrinol Metab 2000; 278: E892-E901.
30. Cammisotto PG, Bukowiecki LJ: Role of calcium in the secretion of leptin from white adipocytes. Am J Physiol Regul Integr Comp Physiol 2004; 287: R1380-R1386.
31. Lammert A, Kiess W, Bottner A et al.: Soluble leptin receptor represents the main leptin binding activity in human blood. Biochem Biophys Res Commun 2001; 283: 982-988.
32. Chan JL, Bluher S, Yiannakouris N et al.: Regulation of circulating soluble leptin receptor levels by gender, adiposity, sex steroids, and leptin: observational and interventional studies in humans. Diabetes 2002; 51: 2105-2112.

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