Serum Levels of the Adipokine Vaspin in Relation to Metabolic and Renal Parameters

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Context: Recently, vaspin was identified as an insulin-sensitizing adipokine. However, regulation of this adipocyte-secreted factor in human disease has not been determined.

Objective: We investigated vaspin serum concentrations in diabetic and nondiabetic patients on chronic hemodialysis (CD) as compared with controls with a glomerular filtration rate (GFR) above 50 ml/min.

Design: Vaspin was quantified by ELISA in control (n = 60) and CD (n = 60) patients and correlated to clinical and biochemical measures of renal function, glucose, and lipid metabolism, as well as inflammation, in both groups.

Results: Mean serum vaspin concentrations were not significantly different between CD patients and controls. Circulating vaspin was significantly lower in males (0.6 ± 0.9 μg/liter) as compared with females (1.3 ± 1.5 μg/liter) and was decreased in insulin-treated subjects. In univariate analyses, vaspin levels positively correlated with age and high-density lipoprotein cholesterol and negatively with waist-to-hip ratio and GFR in control patients, whereas the adipokine was negatively associated with GFR and C-reactive protein (CRP) in CD patients. In multivariate analyses, age and gender were independently associated with vaspin in controls, whereas gender, GFR, and CRP independently predicted circulating vaspin in CD patients.

Conclusions: Vaspin levels are significantly higher in women, and gender is an independent predictor of circulating vaspin in both control and CD patients. In addition, age independently predicts vaspin in control patients, whereas GFR and CRP are independently associated with this adipokine in CD patients. In contrast, circulating vaspin is not independently associated with markers of glucose and lipid metabolism. **(*J Clin Endocrinol Metab* 93: 247–251, 2008)**

Obesity is a rapidly growing disorder in industrialized countries that is associated with insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension (1, 2). When weight is gained, hyperplasia and hypertrophy of adipocytes within adipose tissue are found (1, 2). In recent years it could be demonstrated convincingly that fat cells differentially secrete various proteins, so-called adipokines, which link obesity with components of the metabolic syndrome (1, 2). Furthermore, there is an increasing body of evidence that adipokine dysregulation significantly contributes to the increased risk of cardiovascular disease in obesity (1, 2).

Recently Hida *et al.* (3) characterized vaspin as an interesting novel adipokine with insulin-sensitizing effects. Vaspin belongs to the serine protease inhibitor (serpine) superfamily and is produced in the visceral adipose tissue depot of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of obesity with T2DM (3). The authors demonstrated convincingly in the initial report that administration of vaspin to obese mice improved

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Abbreviations: BMI, Body mass index; CD, chronic hemodialysis; CRP, C-reactive protein; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; OLETF, Otsuka Long-Evans Tokushima Fatty; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio.

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glucose tolerance and insulin sensitivity (3). Furthermore, dysregulated expression of insulin sensitivity-modulating genes in adipose tissue including adiponectin and leptin was reversed after vaspin treatment (3). Moreover, vaspin production was down-regulated with worsening of T2DM in OLETF rats (3). In addition, we have recently shown that induction of vaspin mRNA expression in human adipose tissue is regulated in a fat depot-specific manner and could be associated with parameters of obesity, insulin resistance, and glucose metabolism (4).

The connection between circulating levels of vaspin and components of the metabolic syndrome has not been determined. We hypothesized that circulating vaspin concentrations are linked to markers of insulin sensitivity and obesity. Furthermore, renal elimination has been established as a major route by which physiological levels of various adipokines including adiponectin (5) and leptin (6) are maintained. In contrast, the association between vaspin and renal dysfunction has not been studied so far. We determined vaspin serum levels in patients on chronic hemodialysis (CD) and controls with a glomerular filtration rate (GFR) above 50 ml/min and correlated concentrations of this adipokine to clinical and biochemical measures of renal function, glucose, and lipid metabolism, as well as inflammation, in both groups.

Subjects and Methods

Subjects

A total of 120 Caucasian men (n = 62) and women (n = 58) were recruited with 60 patients having a GFR above 50 ml/min (controls) as assessed by Cockroft-Gault formula and 60 patients being on CD. Body mass index (BMI) was calculated as weight divided by squared height and BMI ranged from 18.7 to 46.1 kg/m^2. Waist-to-hip ratio (WHR) was calculated after waist and hip circumferences were measured. The study population was between 32 and 85 yr old. Thirty controls and 32 CD patients had T2DM defined as fasting blood glucose 126 mg/dl or greater or use of insulin or oral hypoglycemic medications. Diabetes mellitus was excluded in the control group by performing 75-g oral glucose tolerance tests. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described (7). Patients with severe conditions including generalized inflammation or end-stage malignant diseases were excluded from the study. The study was approved by the local ethics committee, and all subjects gave written informed consent before taking part in the study.

Assays

Blood samples were taken after an overnight fast, and serum was immediately frozen and stored in aliquots at −80 C. All samples were thawed two or fewer times before the assays were performed. Each single assay was performed with samples that had undergone an identical number of freezing-thawing cycles. Serum insulin concentrations were determined with a two-site chemiluminescent enzyme immunometric assay for the Immulite automated analyzer (Diagnostic Products, Los Angeles, CA). Adiponectin (Mediagnost, Reutlingen, Germany) and vaspin (Adipogen, Seoul, South Korea) serum levels were measured with commercially available ELISAs according to the manufacturers' instructions. The sensitivity of the vaspin ELISA was 0.01 μg/liter. Whereas the degree of precision of the ELISA system in terms of coefficient of variance (percent) of intraassay was between 1.3 and 3.8%, and that of interassays was between 3.3 and 9.1%. Spike recovery and linearity were in a range of 90–107 and 100–109%, respectively. Specificity was determined using human adiponectin, retinol-binding protein 4, visfatin, plasminogen activator inhibitor-1, TNF-α, resistin-like molecule-β, fatty acid binding protein 4, angiopoietin-like protein 6, glutathione peroxidase 3, progranulin, mouse adiponectin, and mouse resistin. Furthermore, the ELISA was specific for human vaspin and did not cross-react with mouse and rat sera. Serum creatinine, PTH, free fatty acids, cholesterol, triglycerides, and C-reactive protein (CRP) were measured by standard methods in a certified laboratory.

Statistical analysis

For statistical analysis, SPSS software (version 11.5; SPSS, Chicago, IL) was used. Differences between groups were assessed with the use of Mann-Whitney *U* test, Kruskal-Wallis test with Bonferroni *post hoc* analysis, and χ^2 test, as indicated in the table legends. Correlations were performed using the Spearman's rank correlation method. To adjust the effects of covariates and identify independent relationships, multivariate linear regression analyses were performed. Here distribution was tested for normality using Shapiro-Wilk W test, and nonnormally distributed parameters were logarithmically transformed before performing multivariate analyses. $P < 0.05$ was considered as statistically significant in all analyses.

Results

Vaspin serum concentrations are higher in women but not altered in CD

Clinical characteristics of the subgroups studied (control, CD) divided into nondiabetic and diabetic subjects are presented in Table 1. Mean ± SD serum vaspin was 1.0 ± 1.3 μg/liter (range 0.01–9.3 μg/liter) in the total sample and was not significantly different between control (1.0 ± 1.1 μg/liter) and CD (0.9 ± 1.5 μg/liter) patients. Mean circulating vaspin levels were significantly higher in females (1.3 ± 1.5 μg/liter), compared with males (0.6 ± 0.9 μg/liter) ($P < 0.01$). Vaspin serum concentrations were not significantly different between normal-weight (1.2 ± 1.9 μg/liter) and overweight/obese (0.9 ± 1.0 μg/liter) subjects as well as between diabetic (0.8 ± 1.0 μg/liter) and nondiabetic (1.1 ± 1.5 μg/liter) patients. However, patients on insulin treatment showed significantly lower levels of circulating vaspin (0.5 ± 0.4 μg/liter), compared with subjects without insulin (1.2 ± 1.5 μg/liter) ($P < 0.01$). In contrast, significant differences in circulating vaspin could not be detected, depending on oral antidiabetics, β-blockers, angiotensin-converting enzyme/angiotensin II type 1 inhibitors, statins, low-dose aspirin, and erythropoietin (data not shown). When the two subgroups (control, CD) were studied separately, mean vaspin serum levels were increased in females, compared with males in both groups (control: 1.2 ± 1.2 *vs.* 0.6 ± 1.0 μg/liter; CD: 1.4 ± 2.0 *vs.* 0.6 ± 0.8 μg/liter) ($P < 0.01$) (Fig. 1). Again, circulating vaspin was not significantly different, depending on T2DM in control and CD patients (Table 1). Furthermore, vaspin serum levels were not significantly different in control *vs.* CD patients and/or diabetic *vs.* nondiabetic subjects when men and women were studied separately (data not shown). All subsequent analyses were performed in all patients as well as in the two subgroups (control, CD) separately.

Univariate correlations

When all subjects were studied, vaspin concentrations positively correlated with high-density lipoprotein (HDL) choles-

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TABLE 1. Baseline characteristics of the study population divided into controls without diabetes (control/T2DM−) or with diabetes (control/T2DM+) and CD patients without diabetes (CD/T2DM−) or with diabetes (CD/T2DM+)

	Control/T2DM−	Control/T2DM+	CD/T2DM−	CD/T2DM+
n	30	30	28	32
Vaspin (μg/liter)	1.1 ± 1.3	0.8 ± 0.9	1.1 ± 1.8	0.8 ± 1.1
Age (yr)	61 ± 11	63 ± 10	60 ± 14	67 ± 10
Gender (male/female)	11/19	16/14	15/13	20/12
BMI (kg/m^2)	29.8 ± 5.8	30.6 ± 5.2	26.1 ± 5.1[a,b]	28.2 ± 5.0
WHR	0.9 ± 0.1	0.9 ± 0.1[a]	0.9 ± 0.1	1.0 ± 0.1[a]
SBP (mm Hg)	126 ± 16	129 ± 12	123 ± 24	123 ± 21
DBP (mm Hg)	75 ± 11	72 ± 9	72 ± 12	69 ± 9
Creatinine (μmol/liter)	77 ± 15	75 ± 18	780 ± 272[a,b]	743 ± 271[a,b]
GFR (ml/min)	94 ± 32	107 ± 39	10 ± 5[a,b]	10 ± 4[a,b]
PTH (pmol/liter)	4.4 ± 1.7	3.8 ± 1.3	24.1 ± 25.9[a,b]	20.4 ± 13.6[a,b]
FG (mmol/liter)	5.2 ± 0.8	7.8 ± 2.6[a]	4.7 ± 0.9[b]	6.2 ± 2.7[b,c]
FI (pmol/liter)	45.8 ± 26.2	74.0 ± 94.5	56.4 ± 81.7	88.9 ± 126.8
HOMA-IR	1.6 ± 1.0	3.4 ± 3.0	1.9 ± 3.1[b]	4.5 ± 9.4
FFA (mmol/liter)	0.5 ± 0.2	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.4
Cholesterol (mmol/liter)	5.5 ± 0.8	4.9 ± 1.2	4.5 ± 1.0[a]	4.3 ± 1.1[a]
HDL cholesterol (mmol/liter)	1.4 ± 0.3	1.3 ± 0.4	1.1 ± 0.3[a,b]	1.0 ± 0.3[a,b]
LDL cholesterol (mmol/liter)	3.5 ± 0.7	2.9 ± 1.0[a]	2.7 ± 0.9[a]	2.3 ± 0.9[a,b]
TG (mmol/liter)	1.2 ± 0.5	1.7 ± 1.0	1.7 ± 0.5[a]	2.4 ± 1.7[a]
Adiponectin (mg/liter)	7.6 ± 4.1	5.8 ± 3.4	17.3 ± 10.8[a,b]	15.5 ± 11.4[a,b]
CRP (mg/liter)	3.9 ± 3.3	3.3 ± 2.5	14.0 ± 25.9	17.9 ± 24.8[a,b]
Insulin treatment (%)	0 (0)	18 (60)[a]	0 (0)[b]	22 (69)[a,c]
Sulfonylurea (%)	0 (0)	11 (37)[a]	0 (0)[b]	4 (13)[b]
Metformin (%)	0 (0)	21 (70)[a]	0 (0)[b]	0 (0)[b]
TZDs (%)	0 (0)	2 (7)	0 (0)	0 (0)
β-Blocker (%)	8 (27)	19 (63)[a]	16 (57)[a]	25 (78)[a]
ACE/AT1-I (%)	8 (27)	19 (63)[a]	20 (71)[a]	20 (63)[a]
Statin (%)	7 (23)	16 (53)[a]	11 (39)	17 (53)[a]
Low-dose aspirin (%)	2 (7)	9 (30)[a]	7 (25)	13 (41)[a]

Means ± SD or the total number and percentage of patients taking a medication are shown. Continuous parameters were analyzed by Kruskal-Wallis test, followed by Bonferroni *post hoc* analysis, and categorical parameters were analyzed using the χ^2 test. DBP, Diastolic blood pressure; FFA, free fatty acids; FG, fasting glucose; FI, fasting insulin; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; TZD, thiazolidinedione; ACE, angiotensin-converting enzyme; AT1, angiotensin II type 1.

[a] Indicates $P < 0.05$ as compared with control/T2DM−.

[b] Compared with control/T2DM+.

[c] Compared with CD/T2DM−.

terol (r = 0.236, $P = 0.010$), whereas a negative association was observed with WHR (r = −0.299, $P = 0.001$). In controls, serum vaspin levels correlated positively with age (r = 0.354, $P = 0.006$) and HDL cholesterol (r = 0.321, $P = 0.012$) and negatively with WHR (r = −0.349, $P = 0.006$) and GFR (r = −0.375, $P = 0.003$). In CD patients, a positive correlation between circulating vaspin and creatinine was found (r = 0.277, $P = 0.032$). Furthermore, vaspin was negatively associated with GFR (r = −0.397, $P = 0.002$) and CRP (r = −0.340, $P = 0.008$) in these patients. In the groups studied, vaspin did not correlate with markers of insulin sensitivity and glucose metabolism including fasting glucose, fasting insulin, HOMA-IR, and adiponectin (data now shown).

Multivariate correlations

Multiple regression analysis revealed that age, gender, and insulin treatment remained independently associated with vaspin concentrations after adjustment for WHR and HDL cholesterol when all 120 patients were analyzed ($P < 0.05$) (Table 2). Age and gender significantly predicted serum vaspin levels in control patients ($P < 0.05$), whereas the correlations with WHR, HDL cholesterol, and GFR seen in univariate analyses were all lost (Table 2). In CD patients, gender remained independently associated with circulating vaspin ($P < 0.05$) (Table 2). Additionally, GFR and CRP independently predicted serum vaspin in this subgroup ($P < 0.05$) (Table 2).

Discussion

In the current study, we demonstrate for the first time that vaspin serum concentrations are significantly higher in women, compared with men. Furthermore, gender is a significant independent predictor for vaspin serum concentrations not only in controls with a GFR above 50 ml/min, but also CD patients. Interestingly, a gender-dependent regulation has also been demonstrated for adiponectin (8) and leptin (9, 10). Here an inhibitory effect of androgens on expression of both adipokines could be established (8, 11, 12). Furthermore, it is quite possible that estrogens might increase circulating vaspin levels. It is interesting to note in this context that an estrogen-mediated up-regulation has been shown for the adipokine leptin (13). However, it needs

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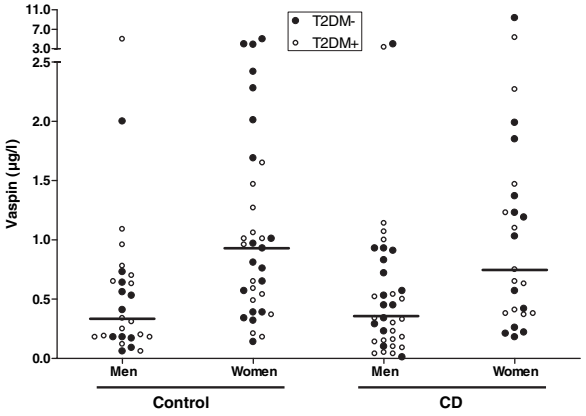

FIG. 1. Vaspin serum levels depend on gender. Individual vaspin serum concentrations in men and women are depicted in control and CD patients. Furthermore, nondiabetic subjects are represented by the *filled circles*, whereas T2DM patients are represented by *open circles*. Median vaspin serum concentrations in men and women in both groups (control, CD) are also shown.

to be pointed out that most women in the study population were postmenopausal, and, therefore, estrogens alone probably do not explain the gender difference in vaspin serum levels. In addition, gender-dependent differences in adipose tissue mass and distribution might contribute to increased circulating vaspin concentrations in women, compared with men.

In the present study, we demonstrate that circulating vaspin is negatively correlated with GFR in univariate analyses in both controls and CD patients. However, this association is lost in controls after adjusting for age and gender. Furthermore, serum vaspin levels are indistinguishable between controls and patients on CD. These results indicate that renal excretion is probably not a major route of vaspin elimination. In contrast to vaspin, other fat-secreted factors including adiponectin (5), leptin (6), and visfatin (14) are primarily eliminated through the kidneys, and higher levels of theses adipokines are found in CD. Furthermore, the adipocyte-secreted factor leptin has been suggested to contribute to CD-associated malnutrition (15). Because vaspin serum levels are indistinguishable between CD and control patients and do not correlate with BMI and WHR in subjects on CD, our data do not support the hypothesis that this adipokine plays a role in CD-linked malnutrition.

In the current report, we demonstrate that age is positively and independently correlated with circulating vaspin in controls but not CD patients. Furthermore, CRP is an independent negative predictor of vaspin concentrations only in CD patients. It is unknown at present whether inflammatory status directly modulates vaspin levels in patients with renal failure.

Interestingly, vaspin serum levels are significantly decreased in insulin-treated subjects. Furthermore, we show that insulin treatment is an independent predictor of vaspin serum levels in our study population. However, the effect of insulin administration on vaspin synthesis in fat and circulating vaspin levels in humans has not been studied so far. It is interesting to note in this context that Hida *et al.* (3) described a differential effect of insulin on vaspin expression in fat of rodents, depending on the depot studied. Thus, the authors demonstrated that insulin treatment of OLETF rats induces vaspin synthesis in sc white adipose tissue, whereas a reduction is found in visceral fat (3). Furthermore, insulin treatment up-regulates circulating vaspin in these animals at 50 but not 30 wk of age (3).

In the present study, vaspin serum levels do not correlate with markers of insulin sensitivity and glucose metabolism including fasting glucose, fasting insulin, HOMA-IR, and adiponectin. Furthermore, the negative association with WHR and the positive correlation with HDL cholesterol seen in control patients in univariate analysis are lost after adjustment for age and gender. In contrast to vaspin, the other insulin-sensitizing adipokine adiponectin (16) is significantly and negatively correlated with HOMA-IR in our study population independent of age and gender in both control and CD patients (data not shown). Taking these findings into consideration, our results do not support the hypothesis that vaspin is a major insulin-sensitizing adipokine in humans besides adiponectin.

TABLE 2. Multivariate linear regression analyses in all subjects, controls, and CD patients with circulating vaspin as dependent variable

Independent variable	β	*P* value
All subjects		
Age	0.192	0.027[a]
Gender	0.294	0.005[a]
Insulin treatment	−0.192	0.031[a]
WHR	−0.085	0.441
HDL cholesterol	0.051	0.574
Controls		
Age	0.333	0.048[a]
Gender	0.362	0.033[a]
Insulin treatment	−0.045	0.720
WHR	−0.058	0.760
HDL cholesterol	0.026	0.853
GFR	−0.029	0.864
CD patients		
Age	0.055	0.637
Gender	0.272	0.019[a]
Insulin treatment	−0.122	0.317
GFR	−0.259	0.043[a]
CRP	−0.313	0.010[a]

Independent variables tested include age, gender, and insulin treatment as well as parameters showing a significant correlation with vaspin levels in univariate analyses. The dependent variable was vaspin.

[a] Indicates significant correlation.

Acknowledgments

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References

1. **Fasshauer M, Paschke R** 2003 Regulation of adipocytokines and insulin resistance. Diabetologia 46:1594–1603
2. **Trujillo ME, Scherer PE** 2006 Adipose tissue-derived factors: impact on health and disease. Endocr Rev 27:762–778
3. **Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, Shikata K, Hourai S, Futami J, Watanabe E, Matsuki Y, Hiramatsu R, Akagi S, Makino H, Kanwar YS** 2005 Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. Proc Natl Acad Sci USA 102:10610–10615
4. **Kloting N, Berndt J, Kralisch S, Kovacs P, Fasshauer M, Schon MR, Stumvoll M, Bluher M** 2006 Vaspin gene expression in human adipose tissue: association with obesity and type 2 diabetes. Biochem Biophys Res Commun 339:430–436
5. **Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y** 2002 Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 13:134–141
6. **Merabet E, Dagogo-Jack S, Coyne DW, Klein S, Santiago JV, Hmiel SP, Landt M** 1997 Increased plasma leptin concentration in end-stage renal disease. J Clin Endocrinol Metab 82:847–850
7. **Fasshauer M, Bluher M, Stumvoll M, Tonessen P, Faber R, Stepan H** 2007 Differential regulation of visfatin and adiponectin in pregnancies with normal and abnormal placental function. Clin Endocrinol (Oxf) 66:434–439
8. **Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda M, Kondo H, Furuyama N, Kihara S, Nakamura T, Tochino Y, Funahashi T, Matsuzawa Y** 2002 Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 51:2734–2741
9. **Horn R, Geldszus R, Potter E, von zur MA, Brabant G** 1996 Radioimmunoassay for the detection of leptin in human serum. Exp Clin Endocrinol Diabetes 104:454–458
10. **Ma Z, Gingerich RL, Santiago JV, Klein S, Smith CH, Landt M** 1996 Radioimmunoassay of leptin in human plasma. Clin Chem 42:942–946
11. **Kapoor D, Clarke S, Stanworth R, Channer KS, Jones TH** 2007 The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. Eur J Endocrinol 156:595–602
12. **Tsou PL, Jiang YD, Chang CC, Wei JN, Sung FC, Lin CC, Chiang CC, Tai TY, Chuang LM** 2004 Sex-related differences between adiponectin and insulin resistance in schoolchildren. Diabetes Care 27:308–313
13. **Shimizu H, Shimomura Y, Nakanishi Y, Futawatari T, Ohtani K, Sato N, Mori M** 1997 Estrogen increases *in vivo* leptin production in rats and human subjects. J Endocrinol 154:285–292
14. **Axelsson J, Witasp A, Carrero JJ, Qureshi AR, Suliman ME, Heimburger O, Barany P, Lindholm B, Alvestrand A, Schalling M, Nordfors L, Stenvinkel P** 2007 Circulating levels of visfatin/pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. Am J Kidney Dis 49:237–244
15. **Young GA, Woodrow G, Kendall S, Oldroyd B, Turney JH, Brownjohn AM, Smith MA** 1997 Increased plasma leptin/fat ratio in patients with chronic renal failure: a cause of malnutrition? Nephrol Dial Transplant 12:2318–2323
16. **Fasshauer M, Paschke R, Stumvoll M** 2004 Adiponectin, obesity, and cardiovascular disease. Biochimie (Paris) 86:779–784

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