

Serum Levels of the Adipokine Chemerin in Relation to Renal Function

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OBJECTIVE— To investigate serum levels of the adipokine chemerin in patients on chronic hemodialysis (CD) as compared with control patients with a glomerular filtration rate (GFR) >50 ml/min.

RESEARCH DESIGN AND METHODS— Chemerin was quantified by ELISA in control patients ($n = 60$) and CD patients ($n = 60$) and correlated with clinical and biochemical measures of renal function, glucose, and lipid metabolism, as well as inflammation, in both groups.

RESULTS— Median serum chemerin levels were more than twofold higher in CD patients (542.2 $\mu\text{g/l}$) compared with subjects with a GFR >50 ml/min (254.3 $\mu\text{g/l}$) ($P < 0.001$). Furthermore, GFR, as assessed by the original Modification of Diet in Renal Disease formula, independently predicted circulating chemerin concentrations in multiple regression analyses in both control patients ($P < 0.05$) and CD patients ($P < 0.01$).

CONCLUSIONS— We demonstrate that markers of renal function are independently related to circulating chemerin levels.

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Recently, chemerin has been identified as a novel adipocyte-secreted factor playing a crucial role in adipocyte differentiation and insulin signaling (1–4). Several studies have quantified circulating chemerin in humans. Thus, two reports found an independent association between chemerin and markers of inflammation (5,6). Furthermore, correlations between circulating chemerin and metabolic syndrome-related parameters have been described (6–8). In contrast to other adipokines (9–12), no data have been published so far about the relation of chemerin to renal function.

RESEARCH DESIGN AND METHODS

Subjects

The design of the study has recently been described in detail (9–12). Briefly, 120 Caucasian men ($n = 62$) and women ($n =$

58) were recruited with 60 patients having a glomerular filtration rate (GFR) >50 ml/min (control patients), as assessed by the original Modification of Diet in Renal Disease formula (13), and 60 patients being on hemodialysis. Thirty control patients and 32 chronic hemodialysis (CD) patients had type 2 diabetes. Patients with active inflammatory diseases including pneumonia, urinary tract infection, endocarditis, sinusitis, and cholangitis were excluded from the study. Furthermore, patients with end-stage malignant diseases of any origin were excluded. Inactive systemic lupus erythematoses, stable coronary heart disease, and previous stroke were not exclusion criteria. 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. In CD patients, blood was

drawn just before hemodialysis started. Chemerin (BioVendor, Modrice, Czech Republic) (intraassay coefficient of variation [CV] 5.1–7.0%, interassay CV 6.9–8.3%), adiponectin (Mediagnost, Reutlingen, Germany) (intraassay CV <4.7%, interassay CV <6.7%), and leptin (Mediagnost, Reutlingen, Germany) (intraassay and interassay CV <10%) were determined with ELISAs according to the manufacturers' instructions. Free fatty acids, cholesterol, triglycerides, C-reactive protein (CRP), insulin, and other routine laboratory parameters were measured in a certified laboratory.

Statistical analysis

SPSS software version 15.0 (SPSS, Chicago, IL) was used for all statistical analyses as further specified in the RESULTS section and in the legend for Table 1. Distribution was tested for normality using Shapiro-Wilk W test, and non-normally distributed parameters were logarithmically transformed before multivariate analyses.

RESULTS

Chemerin serum levels are increased in CD patients

Table 1 summarizes clinical characteristics of the subgroups studied (control and CD). In Table 1 and throughout the text, all continuous variables are given as median \pm interquartile range. Median circulating chemerin was more than twofold higher in CD patients (542.2 \pm 98.1 $\mu\text{g/l}$) compared with control patients (254.3 \pm 88.7 $\mu\text{g/l}$, $P < 0.001$) (Table 1). In contrast, a significant difference in chemerin concentrations could not be demonstrated depending on sex (female subjects 324.4 \pm 284.6 $\mu\text{g/l}$ and male subjects 443.6 \pm 315.2 $\mu\text{g/l}$) and type 2 diabetes (type 2 diabetes 388.1 \pm 303.7 $\mu\text{g/l}$ and non-type 2 diabetes 331.0 \pm 274.6 $\mu\text{g/l}$). CD patients had a significantly lower BMI compared with that in control patients ($P < 0.05$) (Table 1).

Univariate correlations

Using the Spearman rank correlation method, serum chemerin concentrations positively correlated with BMI ($r = 0.398$, $P = 0.002$), fasting insulin (FI) ($r =$

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Table 1—Baseline characteristics of the study population

	Control patients	CD
n	60	60
Chemerin ($\mu\text{g/l}$)	254.3 \pm 88.7	542.2 \pm 98.1*
Age (years)	63 \pm 17	67 \pm 18
Sex (male/female)	27/33	35/25
Diabetic/Nondiabetic	30/30	32/28
BMI (kg/m^2)	28.7 \pm 5.2	27.0 \pm 7.5*
SBP (mmHg)	125 \pm 21	120 \pm 29
DBP (mmHg)	75 \pm 12	70 \pm 20
GFR (ml/min)	87 \pm 29	7 \pm 4*
FG (mmol/l)	5.8 \pm 2.6	4.8 \pm 1.7*
FI (pmol/l)	47.7 \pm 47.7	38.3 \pm 61.8
HOMA-IR	1.8 \pm 2.2	1.1 \pm 2.5
FFA (mmol/l)	0.5 \pm 0.2	0.7 \pm 0.5
Cholesterol (mmol/l)	5.1 \pm 1.1	4.3 \pm 1.3*
HDL (mmol/l)	1.3 \pm 0.4	1.0 \pm 0.5*
LDL (mmol/l)	3.1 \pm 1.1	2.4 \pm 1.0*
Triglycerides (mmol/l)	1.3 \pm 0.8	1.6 \pm 1.3*
Adiponectin (mg/l)	6.3 \pm 4.8	11.9 \pm 15.0*
Leptin ($\mu\text{g/l}$)	17.5 \pm 23.9	20.9 \pm 45.2
CRP (mg/l)	2.6 \pm 4.2	5.0 \pm 18.8*
β -Blocker (%)	27 (45)	41 (68)†
ACE-I/AT1-I (%)	27 (45)	40 (67)†
Calcium channel blocker (%)	14 (23)	19 (32)

Values for median \pm interquartile range or the total number and percentage of patients taking a medication are shown. * $P < 0.05$ as compared with control patients as assessed by Mann-Whitney U test. † $P < 0.05$ as compared with control patients as assessed by χ^2 test. ACE-I, ACE inhibitor; AT1-I, angiotensin AT1 receptor inhibitor; DBP, diastolic blood pressure; FG, fasting glucose; FFA, free fatty acids; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure.

0.408, $P = 0.001$), leptin ($r = 0.516$, $P < 0.001$), and CRP ($r = 0.256$, $P = 0.049$) in control patients. In addition, chemerin negatively correlated with GFR ($r = -0.372$, $P = 0.003$) in control patients. In CD patients, circulating chemerin levels were negatively associated with GFR ($r = -0.413$, $P = 0.001$).

Multivariate regression analyses

Multiple linear regression analysis revealed that GFR (logarithmically transformed [log], standardized β -coefficient = -0.337 , $P = 0.013$) but not FI (log, standardized β -coefficient = 0.186 , $P = 0.128$), leptin (log, standardized β -coefficient = 0.091 , $P = 0.588$), and CRP (log, standardized β -coefficient = 0.138 , $P = 0.236$) remained independently associated with circulating chemerin (log) levels in control patients after adjustment for age (standardized β -coefficient = -0.033 , $P = 0.793$) and sex (standardized β -coefficient = 0.250 , $P = 0.097$). A similar result was obtained when BMI instead of leptin was included in the model (data not shown). In addition, GFR (log, standardized β -coefficient = -0.351 , $P = 0.007$) predicted circulating

chemerin (log) independent of age (standardized β -coefficient = -0.223 , $P = 0.072$) and sex (standardized β -coefficient = -0.076 , $P = 0.546$) in CD patients.

CONCLUSIONS— In the current study, we show for the first time that circulating chemerin levels are more than twofold higher in CD patients compared with control patients. Furthermore, CD is a strong independent predictor of chemerin concentrations in multivariate analysis (data not shown). Moreover, GFR remains independently associated with circulating chemerin in multivariate analysis in both control patients and CD patients. In these cases, functional studies including urine analyses should be performed to define whether renal elimination influences serum levels of chemerin. Furthermore, renal production of chemerin has been shown (1–4), and it should be determined to what extent this kidney-derived chemerin contributes to circulating levels of the adipokine in control patients and CD patients. Moreover, because chemerin modulates inflammation (14,15), its contribution to renal dis-

ease-associated metabolic and vascular complications should be elucidated in future studies.

Recently, an association of chemerin serum levels with metabolic syndrome-related parameters including BMI (5–7), FI (7), triglycerides (6–8), HDL cholesterol (5–8), leptin (5,6), and CRP (5,6) has been shown. In agreement with these findings, chemerin is positively correlated with BMI, FI, leptin, and CRP in univariate analyses in the control patients in our study. However, these associations in control patients are all lost in multivariate analyses after controlling for renal function, whereas GFR remains independently associated with circulating chemerin. Interestingly, GFR also independently predicts chemerin serum levels in the CD patients in our study. These results indicate that renal function is a significant predictor of circulating chemerin not only in subjects with (near) normal glomerular filtration but also in patients with end-stage renal disease.

Some limitations of the study have to be pointed out: First, the study has a cross-sectional design, and, therefore, causality cannot be established. Second, the sample size is relatively small, and it is possible that various nonsignificant associations in multivariate analyses would have become statistically significant if larger samples were studied. Third, differential misclassification of covariates such as type 2 diabetes is possible because type 2 diabetes was only excluded in the control patients but not in the CD patients by 75-g oral glucose tolerance tests due to the necessary fluid restriction in the latter group.

Taken together, our results suggest that renal filtration independently predicts circulating chemerin.

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References

- Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology* 2007;148:4687–4694
- Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Murganandan S, Sinal CJ. Chemerin, a

- novel adipokine that regulates adipogenesis and adipocyte metabolism. *J Biol Chem* 2007;282:28175–28188
3. Roh SG, Song SH, Choi KC, Katoh K, Wittamer V, Parmentier M, Sasaki S. Chemerin: a new adipokine that modulates adipogenesis via its own receptor. *Biochem Biophys Res Commun* 2007;362:1013–1018
 4. Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Kitazawa R, Iida K, Okimura Y, Kaji H, Kitazawa S, Kasuga M, Chihara K. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. *FEBS Lett* 2008;582:573–578
 5. Weigert J, Neumeier M, Wanninger J, Filarsky M, Bauer S, Wiest R, Farkas S, Scherer MN, Schaffler A, Aslanidis C, Scholmerich J, Buechler C. Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. *Clin Endocrinol (Oxf)*. 24 June 2009 [Epub ahead of print]
 6. Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, Leberherz C, Tittus J, Reiser M, Becker C, Goke B, Leber AW, Parhofer KG, Broedl UC. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. *Eur J Endocrinol* 2009;161:339–344
 7. Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, Mahaney MC, Rainwater DL, Vandeberg JL, MacCluer JW, Collier G, Blangero J, Walder K, Jowett J. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. *J Clin Endocrinol Metab* 2009;94:3085–3088
 8. Stejskal D, Karpisek M, Hanulova Z, Svestak M. Chemerin is an independent marker of the metabolic syndrome in a Caucasian population: a pilot study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2008;152:217–221
 9. Ziegelmeier M, Bachmann A, Seeger J, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M. Serum levels of the adipokine RBP-4 in relation to renal function. *Diabetes Care* 2007;30:2588–2592
 10. Ziegelmeier M, Bachmann A, Seeger J, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M. Adipokines influencing metabolic and cardiovascular disease are differentially regulated in maintenance hemodialysis. *Metabolism* 2008;57:1414–1421
 11. Stein S, Bachmann A, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M. Serum levels of the adipokine FGF21 depend on renal function. *Diabetes Care* 2009;32:126–128
 12. Sommer G, Ziegelmeier M, Bachmann A, Kralisch S, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M. Serum levels of adipocyte fatty acid binding protein are increased in chronic haemodialysis. *Clin Endocrinol (Oxf)* 2008;69:901–905
 13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470
 14. Parolini S, Santoro A, Marcenaro E, Luini W, Massardi L, Facchetti F, Communi D, Parmentier M, Majorana A, Sironi M, Tabellini G, Moretta A, Sozzani S. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. *Blood* 2007;109:3625–3632
 15. Cash JL, Hart R, Russ A, Dixon JP, Colledge WH, Doran J, Hendrick AG, Carlton MB, Greaves DR. Synthetic chemerin-derived peptides suppress inflammation through ChemR23. *J Exp Med* 2008;205:767–775