九州大学学術情報リポジトリ
Kyushu University Institutional Repository

Circulating resistin is increased with decreasing renal function in a general Japanese population : The Hisayama Study

Kawamura, Ryoichi
Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University | Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine

Doi, Yasufumi
Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University | Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University

Osawa, Haruhiko
Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine

Ninomiya, Toshiharu
Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University | Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University

他

https://hdl.handle.net/2324/26040

出版情報：Nephrology Dialysis Transplantation. 25 (10), pp.3236-3240, 2010-10. Oxford University Press
バージョン：
権利関係：(C) The Author 2010. Published by Oxford University Press on behalf of ERA-EDTA.

KYUSHU UNIVERSITY

Title: Circulating resistin is increased with decreasing renal function in a general Japanese population: the Hisayama Study

Authors:

Ryoichi Kawamura, M.D.[1, 2], Yasufumi Doi, M.D., Ph.D.[1, 3], Haruhiko Osawa, M.D., Ph.D.[2], Toshiharu Ninomiya, M.D., Ph.D.[1, 3], Jun Hata, M.D., Ph.D.[1, 3], Koji Yonemoto, Ph.D.[1, 3], Yumihiro Tanizaki, M.D., Ph.D.[1, 3], Mitsuo Iida, M.D., Ph.D. [3], Hideichi Makino, M.D., Ph.D.[2], and Yutaka Kiyohara, M.D., Ph.D.[1]

Affiliations:

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[2]Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine, Ehime, Japan

[3]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Corresponding author: Yutaka Kiyohara,

Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Tel: (+81) 92-652-3080

Fax: (+81) 92-652-3075

E-mail: kiyohara@envmed.med.kyushu-u.ac.jp

and Hideichi Makino,

Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine,

Shitsukawa, Toon, Ehime 791-0295, Japan

Phone: +81-89-960-5647

Fax: +81-89-960-5627

E-mail: hidemak@m.ehime-u.ac.jp

Word Count: 2,638 words (including abstract but excluding references, tables, and figures).

Abstract word count: 247

Supplements to the manuscript: 3 tables and a figure

Abstract

Background: The purpose of this study is to investigate the relationship between serum resistin levels and chronic kidney disease (CKD).

Methods: A total of 3,192 community-dwelling subjects (1,377 men, 1,815 women), aged ≥40 years and without renal failure, were divided into four groups according to quartiles of serum resistin concentrations: ≤7.1, 7.2-9.9, 10.0-14.7, and ≥14.8 ng/ml. The associations of resistin levels with renal function status were examined cross-sectionally. The estimated glomerular filtration rate (eGFR) was calculated using the equation from the Modification of Diet in Renal Disease Study, and CKD was defined as an eGFR of <60 ml/min/1.73 m^2.

Results: The age- and sex-adjusted mean values of eGFR decreased significantly with elevating quartiles of resistin (p for trend <0.001). The age- and sex-adjusted odds ratios (ORs) for the presence of CKD increased progressively with higher quartiles of resistin. This trend remained robust even after controlling for age, sex, body mass index, diabetes, homeostasis model assessment of insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), triglycerides, high-density lipoprotein and total cholesterol, hypertension, current smoking, current drinking, and regular exercise (second quartile: OR 1.44, 95% confidence interval [CI] 1.05-1.99; third quartile: OR 2.15, 95% CI 1.58-2.92; fourth quartile: OR 2.32, 95% CI 1.71-3.16; p for trend <0.001). In stratified analyses, high resistin level (≥7.2 ng/ml) was a significant relevant factor in CKD, independent of HOMA-IR or hs-CRP level.

Conclusions: Our findings suggest that elevated resistin level is significantly associated with the likelihood of CKD in the general Japanese population.

Keywords: chronic kidney disease, cross-sectional study, epidemiology, resistin

Introduction

Chronic kidney disease (CKD) is a worldwide public health concern and a major risk factor for end-stage renal disease, cardiovascular disease, and premature death [1]. Identifying and treating risk factors for mild CKD may be the best approach to prevent and delay advanced outcomes [1]. Several epidemiological studies associated age, high blood pressure, diabetes, proteinuria, dyslipidemia, and smoking with the subsequent decline in estimated glomerular filtration rate (eGFR) [2, 3]. It was also reported that insulin resistance and inflammation were emerging risk factors for the occurrence of CKD [4, 5]. However, regardless of the treatment and prevention of these factors, patients with renal failure are increasing in number [6], suggesting the presence of other risk factors.

Resistin belongs to a family of cysteine-rich secretory proteins called resistin-like molecules [7]. In rodents, resistin is derived almost exclusively from fat tissue, and its serum levels are elevated in animal models of obesity and insulin resistance [8]. In humans, on the other hand, resistin is highly expressed in monocytes and macrophages [9]; thus, its pathophysiological role may differ between species. In vitro, resistin activated human endothelial cells, leading to increased expression of adhesion molecules, and induced human aortic muscle cell proliferation [10]. Furthermore, some clinical and epidemiological studies revealed positive correlations between plasma resistin levels and proinflammatory cytokines [11, 12]. A few recent clinical studies also showed an inverse correlation between resistin level and eGFR in CKD patients [13-15]. To date, however, there have been no investigations into the link between serum resistin levels and CKD in large general populations excluding patients with renal failure. The aim of the present study is to examine the relationship between serum resistin levels and CKD in a cross-sectional study of a general Japanese population.

Subjects and Methods

Study population

A population-based prospective study of cardiovascular disease has been under way since 1961 in the town of Hisayama, a suburb of Fukuoka City in southern Japan. As part of this study, in 2002 we conducted a cross-sectional examination among residents of the town. A detailed description of this survey was published previously [16]. Briefly, of all residents aged 40 years or over, 3,328 underwent the examination (participation rate, 77.6%). After excluding 30 subjects who did not consent to participate in the study, 13 subjects with renal failure (eGFR<15 ml/min/1.73 m^2 or treated by dialysis), 82 subjects who had already eaten breakfast on the day serum samples were to be taken, and 11 subjects without serum samples for resistin measurement, the remaining 3,192 subjects (1,377 men, 1,815 women) were enrolled in this study.

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University. Written informed consent was obtained from all participants.

Clinical evaluation and laboratory measurements

At the screening examination, blood samples were collected from an antecubital vein between 8:00 and 10:30 A.M. after at least a 12-hour overnight fast. A portion of each serum specimen was stored at –80°C for 5 years, until 2007, when it was used for the measurement of resistin concentrations by a human resistin enzyme-linked immunosorbent assay kit supplied by R&D Systems (Minneapolis, MN) following the manufacturer's protocol. Linearity was maintained below 0.16 ng/ml, and both intra- and inter-assay coefficient variations were comparable to those specified by the manufacturer (2.6-10.5%). Using fresh blood samples, serum creatinine was measured by the enzymatic method. Levels of triglycerides, high-density

lipoprotein (HDL), and total cholesterol were determined enzymatically. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride, and plasma glucose concentrations were determined by the glucose-oxidase method. Subjects were considered to have diabetes mellitus if they had a fasting plasma glucose level of≥7.0 mmol/l, a 2 -hour postload glucose level of≥11.1 mmol/l, or were taking antidiabetic medications. Serum insulin values were measured by a chemiluminescent enzyme immunoassay. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with the formula: fasting plasma glucose (mmol/l)×fasting serum insulin (μU/ml)/22.5 [17], and subjects in the top quartile of HOMA-IR distribution were defined as having insulin resistance [18]. High-sensitivity C-reactive protein (hs-CRP) levels were quantified using a modification of the Behring Latex-Enhanced CRP assay on a Behring Nephelometer BN-100 (Behring Diagnostics, Westwood, MA). High CRP values were defined as≥1.0 mg/l, according to our previous report [19].

Blood pressure was obtained three times using an automated sphygmomanometer (BP-203RV III; Colin, Tokyo, Japan) with the subjects in a sitting position; the average of the three measurements was used in the present analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current treatment with antihypertensive agents. Height and weight were measured with the subject wearing light clothes without shoes, and body mass index (BMI [kg/m^2]) was calculated.

Each participant completed a self-administered questionnaire covering medical history, smoking habit, alcohol intake, and exercise. The questionnaire was checked by trained interviewers at the screening. Smoking habit and alcohol intake were classified as either current habitual use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times a

week during their leisure time made up a regular exercise group.

Definition of CKD

GFR was estimated by using the following modified equation of the Modification of Diet in Renal Disease (MDRD) Study for Japanese [20]: eGFR (ml/min/1.73 m^2) = 175×(serum creatinine [mg/dl])$^{-1.154}$×(age [years])$^{-0.203}$×(0.741 [Japanese coefficient])×(0.742 if female). Based on the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines [1], we divided kidney function levels into four categories according to eGFR: normal and CKD stage 1 (eGFR ≥90 ml/min/1.73 m^2), CKD stage 2 (eGFR 60-89 ml/min/1.73 m^2), CKD stage 3 (eGFR 30-59 ml/min/1.73 m^2), and CKD stage 4 (eGFR 15-29 ml/min/1.73 m^2). We also determined CKD as a dichotomized category, when eGFR was <60 ml/min/1.73 m^2.

Statistical analysis

SAS software package version 8.2 (SAS Institute, Cary, NC) was used to perform all statistical analyses. Because the distributions of fasting insulin, HOMA-IR, hs-CRP, and triglycerides were skewed, these variables were natural log-transformed for statistical analysis. The subjects were divided into quartiles of resistin concentrations: ≤7.1, 7.2 to 9.9, 10.0 to 14.7, and ≥14.8 ng/ml. The mean values of possible risk factors were adjusted for age and sex using the analysis of covariance and were compared among the resistin quartiles according to the linear regression model. Age- and sex-adjusted means of eGFR among the quartiles were determined by the same method. The frequencies of risk factors were adjusted for age and sex by the direct method using all subjects as a standard population and were tested for trends using logistic regression analysis. The age- and sex- or multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for CKD were also determined by logistic regression analysis.

Results

Table 1 shows the age- and sex-adjusted means or frequencies of potential risk factors according to the quartiles of serum resistin concentrations. The mean values of age, serum creatinine, fasting insulin, HOMA-IR, and hs-CRP, as well as the percentage of men, increased with the quartiles of resistin values, while the mean HDL cholesterol concentration and the frequencies of alcohol intake and regular exercise were negatively correlated with the quartiles. The other variables were not significantly associated with the quartiles.

The left panel in Figure 1 shows the age- and sex-adjusted mean values of eGFR according to the quartiles of serum resistin values. The mean values of eGFR decreased significantly with the quartiles of resistin values (80.4, 76.7, 74.2, and 73.9 ml/min/1.73 m^2, respectively; p for trend <0.001). Meanwhile, the age- and sex-adjusted mean values of serum resistin according to eGFR are shown in the right panel in Figure 1. The age- and sex-adjusted geometric mean values of serum resistin increased significantly as eGFR decreased (9.5 ng/ml in the normal and CKD stage 1, 10.2 ng/ml in CKD stage 2, 11.8 ng/ml in CKD stage 3, and 21.1 ng/ml in CKD stage 4; p for trend <0.001): the differences were significant between normal and CKD stage 1 and CKD stages 2 to 4 (all p<0.001).

Table 2 shows age- and sex-adjusted or multivariate-adjusted ORs and 95% CIs for the presence of CKD according to the resistin quartiles. The age- and sex- adjusted OR for CKD significantly increased with elevating quartiles (p for trend <0.001); compared to the first quartile, OR was greater in the second to fourth quartiles. Such associations were substantially unchanged after adjustment for age, sex, BMI, diabetes, HOMA-IR, hs-CRP, triglycerides, HDL and total cholesterol, hypertension, current smoking, current drinking, and regular exercise (second

quartile: OR 1.44, 95% CI 1.05-1.99; third quartile: OR 2.15, 95% CI 1.58-2.92; fourth quartile: OR 2.32, 95% CI 1.71-3.16).

Finally, we examined the combined as well as separate effects of resistin and HOMA-IR or hs-CRP levels on the presence of CKD (Table 3). When a high resistin level was in the second or higher quartile (≥7.2 ng/ml), the age- and sex-adjusted ORs of CKD were significantly higher in subjects with high resistin and low HOMA-IR (<75th percentile) and in subjects with high resistin and high HOMA-IR (≥75th percentile) compared to the reference group, who had low resistin and low HOMA-IR. Similarly, the age- and sex-adjusted risks of CKD were significantly higher in subjects with high resistin levels, independent of hs-CRP levels. These relationships remained robust even after adjusting for the confounding factors named above.

Discussion

Using the large cross-sectional data of a general Japanese population, we demonstrated that serum resistin levels were negatively associated with eGFR, and that the mean values of serum resistin increased even in CKD stage 2. Furthermore, the elevated levels of serum resistin were an independent relevant factor for CKD after controlling for age, sex, BMI, diabetes, HOMA-IR, hs-CRP, triglycerides, HDL and total cholesterol, hypertension, current smoking, current drinking, and regular exercise. In stratified analyses, high resistin levels were associated significantly with the likelihood of CKD in those with low HOMA-IR (<75th percentile) as well as in those with low hs-CRP levels (<1.0 mg/l). These findings suggest that the measurement of resistin values provides additional information on risk factors for CKD.

In a few clinical studies of CKD patients, resistin levels have been shown to be inversely correlated with eGFR [13-15]. Although polypeptides that have molecular weights comparable to

those of resistin are thought to be freely filtered at normal glomerulus [21], subjects with advanced renal impairment might have serum resistin accumulations due to reduced renal clearance: that is, renal dysfunction might cause elevated serum resistin levels. However, the present study showed that resistin levels were significantly raised even in subjects with CKD stage 2 (eGFR of 60-89 ml/min/1.73 m^2), in which polypeptides would be filtered almost normally. In a clinical study of patients with immunoglobulin A glomerulonephritis, serum resistin levels were also significantly higher in subjects with mild renal dysfunction who had a mean GFR of 76 ml/min/1.73m² than in those who had a mean GFR of 114 ml/min/1.73m² [13]. These observations support the hypothesis that resistin potentially plays an important role in the development of CKD.

It has been assumed that resistin's effect is mediated via insulin resistance or inflammation. In our study, serum resistin levels were positively associated with HOMA-IR, but the association between circulating resistin levels and the likelihood of CKD was independent of HOMA-IR, which is in accord with the results of other clinical studies [13, 14, 22]. Thus, insulin resistance may not be a major mediator of the association between resistin levels and the risk of CKD. Meanwhile, the present study also indicated that the association between resistin levels and the likelihood of CKD was unrelated to hs-CRP, though resistin levels were closely associated with those levels. Resistin directly stimulated the expression of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 in human peripheral blood mononuclear cells [23], and increased the expression of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 genes in vascular endothelial cells [10]. Furthermore, a recent clinical study provided evidence that the association between plasma resistin levels and plasma monocyte chemoattractant protein-1 concentrations was independent of hs-CRP levels [24]. Since it has

become apparent that CKD is a state of chronic glomerular inflammation [5], resistin may play an important role in potentiating inflammation in the kidney, irrespective of hs-CRP and other confounding factors.

There are a variety of methods for estimating GFR. Although inulin clearance is the gold standard among these methods, it is difficult to perform in routine practice. During the past decade, a great deal of effort has been devoted to establish an equation for estimating GFR. There is a debate about which equation is optimal for Japanese; the original MDRD Study equation is widely accepted by clinical practitioners, but it may be unsuitable for Asian populations [20]. When some existing equations, such as the original MDRD Study equations [25] or the Cockcroft-Gault formula [26], were used instead of the modified MDRD Study equation for Japanese in our subjects, we also found significant associations between elevated resistin levels and CKD (data not shown). These findings imply a robust association between serum resistin levels and CKD.

A limitation of our study should be discussed. Due to the study's cross-sectional design, we cannot exclude the possibility that hyper-resistinemia is a consequence of CKD, which is a condition of low urine excretion from serum. However, we found significantly increased resistin levels even when eGFR was 60-89 ml/min/1.73 m^2. Thus, we believe that elevated resistin levels are a potential risk factor for the development of CKD.

In conclusion, an elevated resistin level was a significant relevant factor for CKD in a general Japanese population after taking into account other risk factors, including HOMA-IR and hs-CRP. Because of the cross-sectional design of this study, it is still unclear whether or not hyper-resistinemia is a cause of CKD. Further prospective studies are needed to clarify the causative relationship between serum resistin concentrations and CKD.

Acknowledgments

This study was supported in part by Grants-in-Aid for Scientific Research A (No. 18209024) and C (No. 20591063) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and a Health and Labour Sciences Research Grant of the Ministry of Health, Labour and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004). The authors thank the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

Conflict of interest statement

The authors declare no conflict of interest.

References

1. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 2002; 39 (Suppl 1): S1-S266
2. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the Atherosclerosis Risk in Communities Study. Kidney Int 2000; 58: 293-301
3. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. JAMA 2004; 291: 844-850
4. Chen J, Muntner P, Hamm LL, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol 2003; 14: 469-477
5. Landray MJ, Wheeler DC, Lip GY, et al. Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) Study. Am J Kidney Dis 2004; 43: 244-253
6. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 2002; 13 (Suppl 1): S37-S40
7. Steppan CM, Lazar MA. The current biology of resistin. J Intern Med 2004; 255: 439-447
8. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-312
9. Patel L, Buckels AC, Kinghorn IJ, et al. Resistin is expressed in human macrophages and directly regulated by PPARγ activators. Biochem Biophys Res Commun 2003; 300: 472-476
10. Verma S, Li SH, Wang CH, et al. Resistin promotes endothelial cell activation: further

evidence of adipokine-endothelial interaction. Circulation 2003; 108: 736-740

11. Kunnari A, Ukkola O, Päivänsalo M, Kesäniemi YA. High plasma resistin level is associated with enhanced highly sensitive C-reactive protein and leukocytes. J Clin Endocrinol Metab 2006; 91: 2755-2760
12. Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A. Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. Diabetes Care 2004; 27: 2450-2457
13. Kielstein JT, Becker B, Graf S, et al. Increased resistin blood levels are not associated with insulin resistance in patients with renal disease. Am J Kidney Dis 2003; 42: 62-66
14. Axelsson J, Bergsten A, Qureshi AR, et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. Kidney Int 2006; 69: 596-604
15. Nusken KD, Kratzsch J, Wienholz V, et al. Circulating resistin concentrations in children depend on renal function. Nephrol Dial Transplant 2006; 21: 107-112
16. Doi Y, Kubo M, Yonemoto K, et al. Fasting plasma glucose cutoff for diagnosis of diabetes in a Japanese population. J Clin Endocrinol Metab 2008; 93: 3425-3429
17. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419
18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15: 539-553

19. Arima H, Kubo M, Yonemoto K, et al. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama Study. Arterioscler Thromb Vasc Biol 2008; 28: 1385-1391
20. Imai E, Horio M, Nitta K, et al. Modification of the Modification of Diet in Renal Disease (MDRD) Study equation for Japan. Am J Kidney Dis 2007; 50: 927-937
21. Kataoka H, Sharma K. Renal handling of adipokines. Contrib Nephrol 2006; 151: 91-105
22. Ellington AA, Malik AR, Klee GG, et al. Association of plasma resistin with glomerular filtration rate and albuminuria in hypertensive adults. Hypertension 2007; 50: 708-714
23. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005; 174: 5789-5795
24. Aquilante CL, Kosmiski LA, Knutsen SD, Zineh I. Relationship between plasma resistin concentrations, inflammatory chemokines, and components of the metabolic syndrome in adults. Metabolism 2008; 57: 494-501
25. Levey AS, Bosch JP, Lewis JB, et al. 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
26. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41

Table 1. Age- and sex-adjusted mean values or frequencies of risk factors according to quartiles of serum resistin concentrations

	Serum resistin levels (ng/ml)				
Variable	1.5-7.1 (n=788)	7.2-9.9 (n=803)	10.0-14.7 (n=805)	14.8-90.2 (n=796)	P value for trend
Age (years)	59 ± 11	61 ± 12	62 ± 13	64 ± 13	<0.001
Men (%)	38.1	40.4	44.6	49.5	<0.001
BMI (kg/m^2)	23.0 ± 3.4	23.1 ± 3.4	23.0 ± 3.4	23.2 ± 3.4	0.50
Serum creatinine (μmol/l)	59 ± 15	62 ± 15	64 ± 15	65 ± 15	<0.001
Fasting plasma glucose (mmol/l)	6.1 ± 1.3	6.1 ± 1.3	6.0 ± 1.3	6.1 ± 1.3	0.70
Fasting insulin (pmol/l)	44.6 (13.8-144.5)	46.6 (14.5-150.0)	46.3 (14.4-148.7)	49.5 (15.3-160.5)	0.001
Diabetes (%)	16.5	16.8	18.0	18.9	0.45
HOMA-IR	1.66 (0.44-6.29)	1.72 (0.46-6.48)	1.71 (0.45-6.42)	1.83 (0.48-6.94)	0.007
Hs-CRP (mg/l)	0.44 (0.04-4.53)	0.51 (0.05-5.28)	0.54 (0.05-5.49)	0.66 (0.06-6.88)	<0.001
Triglycerides (mmol/l)	1.12 (0.39-3.18)	1.16 (0.41-3.29)	1.14 (0.40-3.23)	1.17 (0.41-3.35)	0.13
HDL-cholesterol (mmol/l)	1.70 ± 0.40	1.61 ± 0.40	1.62 ± 0.40	1.55 ± 0.40	<0.001
Total cholesterol (mmol/l)	5.30 ± 0.90	5.27 ± 0.89	5.31 ± 0.89	5.23 ± 0.90	0.15
Systolic blood pressure (mmHg)	132 ± 20	132 ± 20	132 ± 20	132 ± 20	0.96
Diastolic blood pressure (mmHg)	79 ± 12	79 ± 12	78 ± 12	78 ± 12	0.66
Hypertension (%)	45.0	42.9	43.2	46.3	0.98
Current smoking (%)	20.7	21.5	21.9	22.8	0.29
Current drinking (%)	48.8	44.4	43.4	38.3	<0.001
Regular exercise (%)	11.1	10.4	9.8	8.7	0.04

BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; HDL: high-density lipoprotein. Values are given as means ± SD or frequencies. Age and percentage of men are not adjusted. Fasting insulin, HOMA-IR, hs-CRP, and triglycerides are shown by geometric means and 95% CIs due to the skewed distribution.

Table 2. Age- and sex- or multivariate-adjusted ORs and their 95% CIs for the presence of chronic kidney disease according to quartiles of serum resistin concentrations

	Serum resistin levels (ng/ml)				
	1.5-7.1	7.2-9.9	10.0-14.7	14.8-90.2	p value for trend
Subjects (n)	788	803	805	796	
CKD cases (n)	75	117	166	192	
Age- and sex-adjusted OR (95% CI)	1 (reference)	1.44 (1.06-1.98)	2.15 (1.59-2.90)	2.33 (1.73-3.14)	<0.001
Multivariate-adjusted OR (95% CI)	1 (reference)	1.44 (1.05-1.99)	2.15 (1.58-2.92)	2.32 (1.71-3.16)	<0.001

CKD: chronic kidney disease; OR: odds ratio; CI: confidence interval.

Multivariate adjustment was made for age, sex, body mass index, diabetes, homeostasis model assessment of insulin resistance, high-sensitivity C-reactive protein, triglycerides, high-density lipoprotein and total cholesterol, hypertension, current smoking, current drinking, and regular exercise.

Table 3. Age- and sex- or multivariate-adjusted ORs and their 95% CIs for chronic kidney disease according to the presence or absence of high resistin levels and high HOMA-IR as well as high hs-CRP values

	Subjects, n	CKD cases, n	Age- and sex-adjusted OR (95% CI)	p value	Multivariate-adjusted OR (95% CI)	p value
HOMA-IR						
low + low resistin	602	57	1 (reference)		1 (reference)	
low + high resistin	1,773	340	1.84 (1.35-2.49)	<0.001	1.85 (1.35-2.52)	<0.001
high + low resistin	178	17	1.00 (0.56-1.78)	0.99	0.93 (0.51-1.68)	0.80
high + high resistin	613	131	2.34 (1.66-3.29)	<0.001	2.14 (1.47-3.12)	<0.001
hs-CRP						
low + low resistin	645	53	1 (reference)		1 (reference)	
low + high resistin	1,717	309	2.13 (1.56-2.91)	<0.001	2.12 (1.54-2.91)	<0.001
high + low resistin	143	22	1.69 (0.98-2.92)	0.06	1.62 (0.92-2.84)	0.09
high + high resistin	687	166	2.45 (1.74-3.45)	<0.001	2.46 (1.72-3.50)	<0.001

CKD: chronic kidney disease; HOMA-IR: homeostasis model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; OR: odds ratio; CI: confidence interval.

High resistin levels were defined as the second or higher quartiles of its values; low resistin levels were the first quartile of its values.

HOMA-IR: “high” indicates ≥75th percentile (HOMA-IR ≥2.6); “low” <75th percentile.

Hs-CRP: “high” indicates ≥1.0 mg/l; “low” <1.0 mg/l.

Multivariate adjustment was made for age, sex, body mass index, diabetes, HOMA-IR, hs-CRP, triglycerides, high-density lipoprotein and total cholesterol, hypertension, current smoking, current drinking, and regular exercise, but each risk factor that had been used for categorization was excluded from the confounding factors.

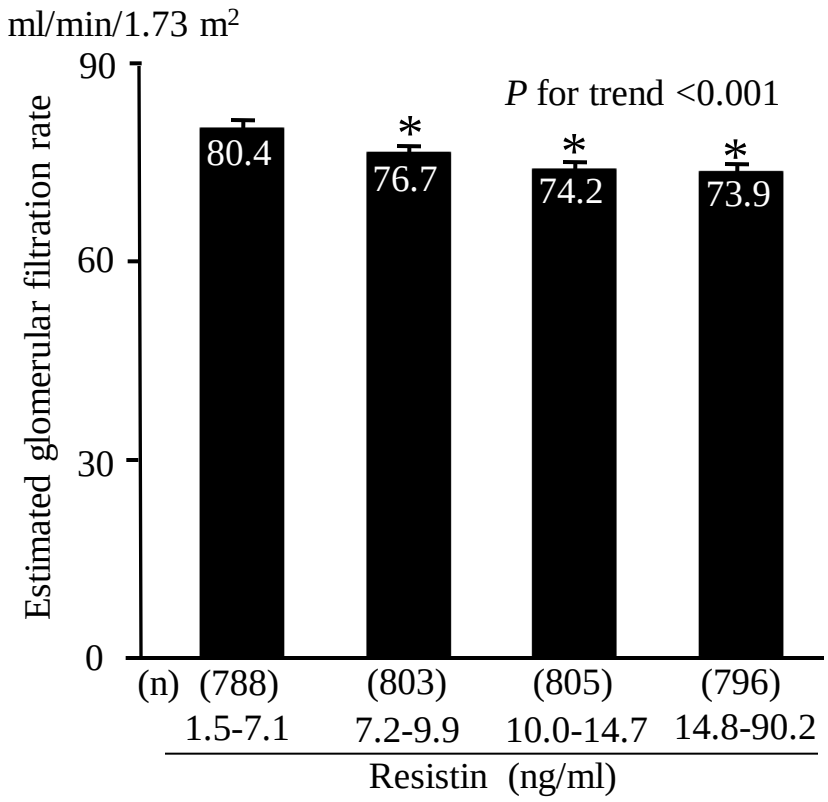
Figure Legends

Figure 1: The age- and sex-adjusted mean values of estimated glomerular filtration rate (eGFR) according to quartiles of serum resistin concentrations (right panel), and the age- and sex-adjusted mean values of serum resistin levels according to eGFR (left panel).

Values are given as means ± standard error.

*$p<0.001$ vs. the first quartile

†$p<0.001$ vs. eGFR of ≥90 ml/min/1.73 m^2


ml/min/1.73 m2
Estimated glomerular filtration rate
90
60
30
0
P for trend <0.001
80.4
76.7
74.2
73.9
*
*
*
(n) (788) (803) (805) (796)
1.5-7.1 7.2-9.9 10.0-14.7 14.8-90.2
Resistin (ng/ml)

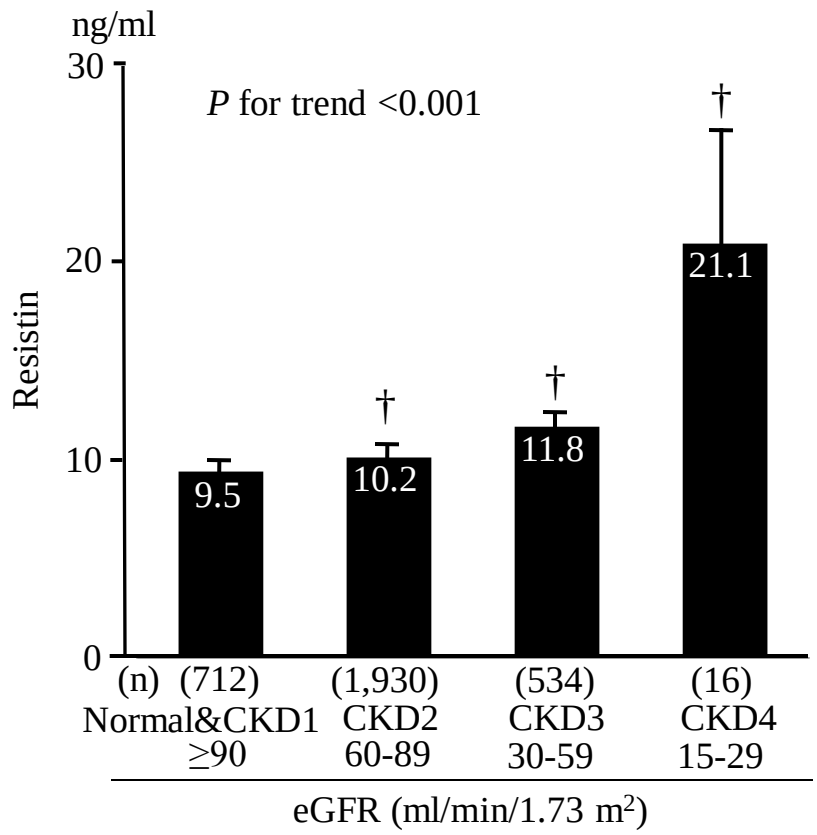

ng/ml
Resistin
30
20
10
0
P for trend <0.001
9.5
10.2
11.8
21.1
†
†
†
(n) (712) (1,930) (534) (16)
Normal&CKD1 CKD2 CKD3 CKD4
≥90 60-89 30-59 15-29
eGFR (ml/min/1.73 m2)

Figure 1