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ORIGINAL PAPER

SIGNIFICANCE OF CIRCULATING ADIPOCYTOKINES IN HYPERTENSIVE PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Introduction. Hypertension (HTN) is both a cause and effect of chronic kidney disease (CKD) and contributes to its progression. Visfatin and resistin, two of the key cytokines secreted by adipocytes, have been shown to be associated with HTN.
The objective of our study was to investigate the association of plasma visfatin and resistin in HTN patients with CKD, after adjusting for multiple important risk factors of CKD.
Materials and Methods. We investigated the association of plasma visfatin and resistin in 55 patients with HTN and CKD and in 55 HTN controls without CKD. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 or presence of albuminuria. Quantile regression and logistic regression models were used to examine the association between adipokines and CKD, adjusting for multiple confounding factors.
Results. Compared to HTN patients without CKD, adjusted median visfatin value (48.0 vs. 22.1 ng/mL, p<0.0001) and adjusted mean resistin value (17.3 vs 9.8 ng/mL, p<0.0001) were significantly higher in HTN patients with CKD. The multiple-adjusted odds ratio (95% confidence interval) of CKD, comparing the highest tertile to the lower two tertiles, was 2.3

Résumé

La signification des adipocytokines circulantes chez les hypertendus avec de l'insuffisance rénale chronique

Introduction. L'hypertension (HTN) est à la fois une cause et un effet de l'insuffisance rénale cronique (IRC) et contribue à sa progression. La visfatine et la résistine, deux des principales cytokines sécrétées par les adipocytes, se sont révélées être associées à la HTN.
L'objectif a été d'étudier l'association de la visfatine plasmatique et de la résistine chez les patients HTN avec CKD après ajustement pour plusieurs facteurs de risque importants pour CKD.
Matériel et méthodes. Nous avons étudié l'association de la visfatine plasmatique et de la résistine chez 55 patients avec HTN avec CKD et chez 55 témoins HTN sans CKD. L'IRC a été définie comme un débit de filtration glomérulaire estimé (DFGe) <60 ml/min/1,73m^2 ou la présence d'albuminurie. Des modèles de régression quantile et de régression logistique ont été utilisés pour examiner l'association entre les adipokines et la CKD en ajustant les facteurs de confusion multiples.
Résultats. Par rapport au patient HTN sans CKD, la visfatine médiane ajustée (48,0 vs 22,1 ng/mL, p

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(1.1, 4.9) for visfatin and 13.8 (7.4, 25.2) for resistin. In addition, higher visfatin and resistin were independently associated with lower eGFR and higher urinary albumin levels.

Conclusions. These findings suggest that adipocytokines are independently and significantly associated with the risk and severity of CKD in HTN patients. Longitudinal studies are warranted to evaluate the prospective relationship of adipocytokines to the development and progression of CKD.

Keywords: chronic kidney disease, hypertension, adypocytokines, visfatin, resistin.

List of abbreviations:
HTN: hypertension
CKD: chronic kidney disease
GFR: glomerular filtration rate
CVD: cardiovascular disease
BMI: body mass index

<0,0001) et la résistine moyenne ajustée (17,3 vs 9,8 ng/mL, p <0,0001) étaient significativement plus élevées chez les patients HTN atteints de CKD. Le rapport de cotes à ajustement multiple (intervalle de confiance à 95%) de l'IRC comparant le tertile le plus élevé aux deux tertiles inférieurs était de 2,3 (1,1, 4,9) pour la visfatine et de 13,8 (7,4, 25,2) pour la résistine. De plus, une visfatine et une résistine plus élevées ont été indépendamment associées à un eGFR inférieur et à des niveaux d'albumine urinaire plus élevés.

Conclusions. Ces résultats suggèrent que les adipocytokines sont associées de manière indépendante et significative au risque et à la gravité de l'IRC chez les patients avec HTN. Des études longitudinales sont justifiées pour évaluer la relation prospective des adipocytokines avec le développement et la progression de l'IRC .

Mots-clés: insuffisance rénale chronique, hypertension, adipocytokines, visfatine, résistine.

Introduction

Hypertension (HTN) is the cause and effect of chronic kidney disease (CKD) and contributes to its progression[1,2]. As glomerular filtration rate (GFR) decreases, the frequency and severity of HTN increase[3]. In addition, HTN and CKD are independent risk factors for cardiovascular disease (CVD). When both coexist, the risks of morbidity and mortality from cardiovascular diseases significantly increase[4].

Adipose tissue, which is known to be a large endocrine organ, plays a role in the regulation of various biological functions, including the secretion of hormones, known as adipokines or adipocytokines[5,6]. In recent years, adipocytokines have become an important part of the multipotential secretory organ, as well as its role in the biology of various organs.

There are different members of adipocytokines with different roles in health and disease[5,7]. Sometimes there are conflicting ideas about the effect of adipocytokines on the pathobiology of kidney disease. It discusses the different roles of each important adipokine.

Visfatin and resistin, two of the key cytokines secreted by adipocytes, have been shown to be associated with CVD. However, the association of these adipocytokines with CKD is unclear.

The objective of the study was to investigate the relationship between plasma visfatin and resistin in patients with HTN with CKD, after adjusting for several important risk factors for CKD. In addition, the relationship between plasma visfatin and resistin and the severity of CKD, as measured by the estimated GFR and albumin in urine, was investigated.

Materials and methods

A total of 110 HTN patients, regularly followed up in the centers of primary care (clinical bases of the Kharkiv Medical Academy of Postgraduate Education) in Kharkiv region from October 2017 to November 2019, were recruited to participate in this observational study. HTN was defined as an average systolic pressure ^{3}140 mm Hg and/or diastolic pressure ^{3}90 mm Hg in at least two visits, and/or the need for antihypertensive therapy. Subjects were divided into two groups: 55 HTN patient with CKD and 55 HTN patients without CKD (control group). They were matched for age, gender and BMI. All individuals were regularly followed up during the first 6 months for drug therapy optimization. Patients were submitted to investigation including adherence to treatment, and secondary forms of HTN were properly observed and excluded.

A standard questionnaire was administered by trained staff at a clinical visit to obtain demographic information, lifestyle risk factors (including cigarette smoking, alcohol drinking, and physical activity), self-reported history of cardiovascular disease, diabetes, hypercholesterolemia, and HTN, as well as medication use.

Three blood pressure measurements were obtained at a clinical visit by trained and certified staff according to a common protocol adapted from procedures recommended by the of the European

Society of Hypertension [ESH] / European Society of Cardiology [ESC] for the treatment of arterial hypertension. The standard mercury sphygmomanometer was used and one of four cuff sizes (pediatric, regular adult, large or thigh) was chosen on the basis of the circumference of the participant's arm. Body height and weight were obtained by trained staff and used to calculate body mass index (BMI=weight in kg/ height^2 in m).

An overnight fasting blood sample was collected to measure plasma visfatin, resistin, and glucose, serum creatinine and cholesterol, and triglycerides.

CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or presence of albuminuria (30 mg/24 h)[3]. The patients were excluded if they had a history of chronic dialysis, kidney transplants, immunotherapy in the past 6 months, chemotherapy within the past 2 years and current clinical trial participation that may have an impact on CKD. Additional exclusion criteria were history of HIV or AIDS and inability or unwillingness to give informed consent. Controls were recruited through mass mailing to residents aged 35–75 years living in the same area according to zip code. The eligibility of controls was assessed by a prescreening telephone interview and the clinic screening visit. Individuals were included if they had no evidence of CKD (eGFR >60 ml/min/1.73 m^2 and no persistent albuminuria). Cases and controls were frequency-matched according to age group (10 years), gender and race to increase the efficiency of patient recruitment and statistical analysis.

The study was conducted in accordance with international standards of bioethics (Council of the European Convention on Human Rights and Biomedicine) and the recommendations of the Committee on Bioethics of the Ministry of Health of Ukraine. All patients signed an informed consent to participate in the study. This study was approved by the Ethics Commission of the Kharkiv Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine (Kharkiv, UA).

Measurements

The standard questionnaire was administered by trained staff at a clinical visit to obtain demographic information, lifestyle risk factors (including cigarette smoking, alcohol drinking and physical activity), self-reported history of CVD, diabetes, hypercholesterolemia and hypertension, as well as the use of antihypertensive, lipid-lowering and antidiabetic medications.

The overnight fasting blood sample was collected to measure serum visfatin and glucose, serum creatinine (SCr) and cholesterol and triglycerides. eGFR was estimated from SCr, sex, age and race using the CKD-Epi equation:

$$GFR = 141 \times min(SCr/k, 1)^{\alpha} \times max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ (if\ female) \times 1.159\ (if\ black),$$

where k is 0.7 and 0.9 and α is –0.329 and –0.411 for females and males, respectively [10]. A 24-hour urinary sample was collected to measure creatinine and albumin.

Serum cholesterol and triglyceride levels were assayed using an enzymatic procedure on the automatic analyzer. Serum glucose was measured using the hexokinase enzymatic method. SCr was measured using the Roche enzymatic method. Serum visfatin was measured with ELISA assay kits. The assay employs the quantitative sandwich enzyme immunoassay technique and all samples were assayed in duplicate. The intraassay and interassay coefficients of variation were 3.6 and 5.7%, respectively.

Statistical Analysis

Medians and interquartile ranges (IQR) for visfatin (ng/mL) was calculated for CKD patients and controls, and the Mann-Whitney test was used to test differences in the unadjusted medians. Quantile regression was used to obtain adjusted medians and IQR, and the Wald test was used to test differences in the adjusted medians between CKD patients and controls. These analyses were adjusted for age, gender, race, high school education, current cigarette smoking, weekly alcohol consumption, regular physical activity ([3]moderate or heavy activities twice per week), BMI, low-density cholesterol (LDL) cholesterol, systolic blood pressure, fasting plasma glucose, and history of cardiovascular disease. All analyses were also conducted adjusting from waist circumference instead of BMI to assess if a particular measure of adiposity has an impact on the results. Means and 95% confidence intervals (CI) were calculated for resistin (ng/mL), a student t-test was used to test for differences in unadjusted means, and ANOVA was used for adjusted means.

Multivariate logistic regression was used to obtain adjusted odds ratios comparing the highest tertile of leptin, resistin, and total adiponectin to the lower two tertiles between CKD patients and controls. Tertiles were defined based upon measurements in the control group. Multivariable linear regression was used to examine the association of eGFR and urinary albumin with visfatin, resistin, after adjustment for the previously mentioned covariates. Multivariate-adjusted regression coefficients are reported associated with a one standard deviation increase in visfatin and resistin.

Table 1. Characteristics of patients with CKD and controls.

Variables	*HTN patients with CKD (n = 55)*	*HTN patients without CKD (n = 55)*	*p value for difference*
Age, years	56.6±8.5	53.1±10.2	0.017
Males, %	53.5	48.2	0.056
High school education, %	62.5	73.2	<0.001
Current cigarette smoking, %	32.8	29.5	0.30
Weekly alcohol drinking, %	26.4	55.1	<0.0001
BMI	32.2±7.8	28.9±6.4	<0.0001
Systolic blood pressure, mmHg	143.1±22.3	131.6±15.4	<0.0001
Diastolic blood pressure, mmHg	83.5±13.5	81.2±9.8	0.75
Plasma glucose, mg/dL	117.8±48.2	105.6±29.7	<0.0001
LDL-cholesterol, mg/dL	102.6±48.3	121.4±32.1	<0.0001
History of CVD, %	39.6	8.2	<0.0001
History of hyperlipidemia, %	85.4	26.7	<0.0001
History of diabetes, %	44.6	6.9	<0.0001
Lipid-lowering medication use, %	24.4	9.8	<0.0001
Anti-diabetic medication use %	33.5	4.6	<0.0001
Aspirin use, %	32.2	7.5	<0.0001
Creatinine, mg/dL	2.2±1.4	0.8±0.3	<0.0001
eGFR, ml/min/1.73 m^2	44.8±16.5	91.6±12.7	<0.0001
Urinary albumin, mg/24 ha	75.6 (13.4–421.5)	6.1 (4.9–10.9)	<0.0001

[a] Median (interquartile range)

Table 2. Adipocytokines' levels according to chronic kidney disease status.

	Unadjusted median (IQR)			*Multivariable-adjusted median (IQR)**		
Adipocytokines	*HTN patientsss with CKD (n = 55)*	*HTN patients without CKD (n = 55)*	*p value for difference*	*HTN patients with CKD (n = 55)*	*HTN patients without CKD (n = 55)*	*p value for difference*
Visfatin, ng/mL	35.2 (22.6, 47.8)	16.5 (18.2, 24.8)	<0.0001	48.0 (29.5, 62.7)	22.1 (10.1, 30.3)	<0.0001
Resistin, ng/mL	17.3 (16.2, 18.5)	9.9 (9.3, 10.6)	<0.0001	17.3 (16.2, 18.3)	9.8 (8.6, 10.1)	<0.0001

IQR = inter-quartile range.
*Adjusted for age, gender, race, high school education, current cigarette smoking, weekly alcohol consumption, body-mass index, LDL-cholesterol, systolic blood pressure, serum glucose, and history of cardiovascular disease.

Results

The general characteristics of study participants with HTN by CKD status are presented in Table 1. People with CKD were older, less educated, heavier and less likely to drink alcohol compared to people without CKD. In addition, they more often had a history of CVD, diabetes, and hyperlipidemia and used lipid lowering, antidiabetes, and aspirin. Systolic blood pressure, plasma glucose and albumin in urine were significantly higher, while LDL cholesterol and GFR were lower in patients with CKD compared with the control group.

The median of visfatin is significantly higher in patients with HTN and CKD compared with the control group (35.2 ng/ml versus 16.5 ng/ml; p <0.0001) and remains significantly higher after full adjustment (table 2). The average value of resistin was also higher in cases than in the control, both adjusted and unadjusted (17.3 vs. 9.9 ng/ml; p <0.0001).

In logistic regression analyzes adjusted for age, gender, and race, individuals with the highest tertile of visfatin and resistin have a significantly higher likelihood of CKD compared to the two lower tertiles (Table 3). Additional adjustments for high school, current cigarette smoking, weekly alcohol consumption, LDL cholesterol, systolic blood pressure, and serum glucose did not significantly change the relationship between visfatin, resistin, and CKD. After further adjustments for BMI, the highest tertiles of visfatin and resistin were reliably associated with CKD compared with the two lower tertiles. The correction for the waist circumference instead of BMI did not significantly change the association. In a final model with additional adjustment for history of CVD, the odds of CKD in the highest tertiles of visfatin and resistin remained significantly higher than the odds in the lower two tertiles.

Multivariate linear regression of visfatin, resistin with GFR and albumin in the urine showed inverse

Table 3. Odds ratios of chronic kidney disease associated with highest tertile compared to the lowest two tertiles adipocytokines.

Adipocytokines	*Age, gender, and race-adjusted*		*Multivariable-adjusted**		*Multivariable-adjusted***		*Multivariable-adjusted****	
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
Visfatin (ng/mL)								
<20.45	1.0 (ref)	<0.0001	1.0 (ref)	0.0002	1.0 (ref)	0.007	1.0 (ref)	0.04
≥20.45	3.94 (2.31, 6.71)		3.21 (1.75, 5.96)		2.78 (1.41, 5.59)		2.34 (1.13, 4.85)	
Resistin (ng/mL)								
<10.53	1.0 (ref)	<0.0001	1.0 (ref)	<0.0001	1.0 (ref)	<0.0001	1.0 (ref)	<0.0001
≥10.53	12.3 (7.6, 19.5)		11.6 (6.8, 21.1)		12.0 (7.2, 21.3)		13.8 (7.4, 25.2)	

*Adjusted for age, gender, race, high school education, current cigarette smoking, weekly alcohol consumption, physical activity, LDL-cholesterol, systolic blood pressure, and serum glucose.
**Additionally adjusted for body mass index.
***Additionally adjusted for history of cardiovascular disease.

Table 4. Multivariable-adjusted regression coefficients (95% confidence intervals) of GFR and urinary albumin associated with one standard deviation difference in adipocytokines

	eGFR, mL/min/1.73 m²		*Log (urinary albumin, mg/24-hrs)*	
	β (95% CI)	*p-value*	*β (95% CI)*	*p-value*
Log (visfatin, 1.25 ng/mL)	–13.8 (–18.5, –9.1)	<0.0001	0.69 (0.39, 0.93)	<0.0001
Resistin (7.65 ng/mL)	–15.5 (–18.2, –12.9)	<0.0001	0.78 (0.58, 0.92)	<0.0001

eGFR = estimated-glomerular filtration rate.
*Adjusted for age, gender, race, high school education, current cigarette smoking, weekly alcohol consumption, body-mass index, LDL-cholesterol, systolic blood pressure, serum glucose, and history of cardiovascular disease.

association with eGFR and a significant positive relationship with albumin and each of adipocytokines (Table 4). The direction of these associations is consistent with the fact that visfatin and resistin are positively associated with the severity of CKD.

The study has some limitations. We did not assess the inflammatory status of the participants. Inflammation is associated with adipocytokines and also with CKD. It is thus possible that the lack of information about the inflammatory status could have caused residual confounding. Also, the cross-sectional nature of the study means that it cannot determine a causal relationship between adipocytokines and CKD.

Discussion

Our study showed that plasma visfatin and resistin levels were significantly higher in HTN patients with CKD compared with the control group without CKD. In addition, there was a strong dose response and a significant relationship between serum visfatin level, resistin level and CKD severity, as measured by GFR and albuminuria, regardless of established risk factors for CKD, including diabetes and CVD. These results can have important clinical implications. A clear understanding of the adipobiology of the disease can help us apply the adipokine approach in pharmacology strategies.

The level of circulating visfatin increases sharply in patients with CKD and is associated with kidney function and soluble vascular cell adhesion molecule (VCAM)-1 as a key marker of endothelial damage[8]. In patients, as well as in animals of the 2 type diabetes model, the level of visfatin is increased. Therefore, visfatin is a pro-inflammatory adipokine in metabolic syndrome and type 2 diabetes[6]. Other studies have shown that the administration of visfatin induces the secretion of pro-inflammatory and profibrotic molecules such as type 1 collagen, an inhibitor of plasminogen activator 1, and TGF-β[8-10].

Yilmaz et al. found that blood levels of visfatin were associated with endothelial dysfunction[11]. Mu et al. reported that a higher level of visfatin is associated with endothelial dysfunction, atherosclerosis, and lipid dysregulation in patients with CKD[12]. Axelsson et al. stated that renal function affects the level of circulating visfatin; however, they were not able to detect any significant association between the markers of insulin resistance and visfatin levels in patients with CKD[13]. Carrero et al. reported that patients with CKD with poor appetite have elevated

levels of visfatin, and this has an unfavorable correlation with fasting triglycerides and serum amino acids[14]. Mahmoud et al. found that, with the exception of a significant positive association between visfatin and CKD levels, there was no difference in visfatin concentration in patients with and without diabetes. In addition, a negative correlation with GFR and a positive correlation with proteinuria was reported[15].

The main source of resistin is visceral adipose tissue-resident macrophage. Resistin has been reported to increase the risk of atherosclerosis, CVD, and insulin resistance diseases[16,17]. An independent association of resistin and GFR in the early stages of hypertension expresses the participation of this protein in the progression of kidney damage. Resistin promotes the expression of adhesion molecules, endothelin and matrix metalloproteinases and stimulates systemic vascular dysfunction, which affects GFR[18,19]. In addition, a positive correlation was revealed between the number of leukocytes, endothelin-1, and CRP with resistin[20].

In patients with CKD, serum resistin levels are negatively associated with GFR[21]. Similarly, Marouga et al. reported that elevated resistin levels are associated with decreased GFR and may be involved in malnutrition and inflammation[22]. Resistin can induce the expression of adhesion molecules such as ICAM-1 and VCAM-1. This induction can be inhibited by adiponectin, ICAM-1, and VCAM-1 using the negative feedback mechanism, as well as other inflammatory markers, such as IL-6 and CRP, which positively correlates with resistin in patients with CKD[21]. In addition, this correlation is observed in patients with renal transplant and in animal models with dietary obesity[23,24].

A molecular experiment showed that resistin via the NFκB pathway can affect the overexpression of inflammatory molecules, including IL-6 and TNF-α[25]. It is reported that in ESKD, resistin increases significantly, which was weakly correlated with inflammation and was not associated with insulin sensitivity and negatively correlated with adiponectin levels. Interestingly, the relationship between resistin levels and all-cause mortality and cardiovascular events depended on adiponectin levels, which means that adiponectin can modulate the inflammatory effect caused by resistin and other inflammatory elements[26].

Conclusions

In conclusion, our results show that visfatin and resistin are associated with the risk and severity of CKD in patients with HTN. These results suggest that longitudinal studies and clinical trials should be performed to determine if adipocytokines play a role in the development and progression of CKD, regardless of BMI or waist circumference. These important findings may improve our understanding of the risk factors for CKD in HTN patients.

Author contributions:

Conceptualization, O.K. and S.K.; methodology, O.K.; software, S.K.; validation, S.K. and A.K.; formal analysis, O.K. and Y.F.; investigation, A.K., Y.F., and S.K.; resources, O.K.; data curation, Y.F. and O.K.; writing – original draft preparation, O.K and Y.F.; writing – review and editing, S.K., O.K. and A.K.; visualization, A.K. and Y.F.; supervision, O.K. and S.K.; project administration, O.K. All the authors read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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