The role of resistin and its relation to other pathogenetic factors of the chronic kidney disease development

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Abstract

Chronic kidney disease (CKD) is the leading cause of death from non-communicable diseases, and its prevalence in 2017 ranged from 8.5 to 9.8%. Depending on the stage of CKD, stage 1 was diagnosed in 3.5%, stage 2 in 3.2% and stage 3 in 7.6%, while stages 4 and 5 took place in 0.4 and 0.1% of the world’s population respectively. Obesity also contributes to the increase in the prevalence and severity of CKD, and their combination occurs in 3.1% of patients. Kidney damage and their structural and functional changes in patients with obesity are associated with high metabolic activity of adipose tissue, due to the synthesis of adipocytokines, including resistin.

The purpose of the work: to study changes of resistin level in the blood in patients with early stages of chronic kidney disease, its relation to the level of endothelin, markers of lipid metabolism and inflammation.

Materials and methods: 70 patients with stage 1 and 88 patients with stage 2 of CKD with different stages of obesity were examined. Glomerular filtration rate (GFR) was calculated by the formula CKD-EPI based on creatinine, cystatin C and their combination (CKD-EPIcysC / cr). The levels of cystatin C, resistin, tumor necrosis factor-alpha (TNF-α) and endothelin-1 were determined by enzyme-linked immunosorbent assay. Determination of total cholesterol and low-density lipoprotein cholesterol levels in the blood serum was performed by colorimetric method. Statistical analysis of the results was performed with the help of Statistica 6.0 statistical software package using Student’s t-test and Spearman’s rank correlation coefficient.

Results: an increase of the resistin level in the blood by 1.3 times in the patients with stage 1 CKD and by 1.6 times in the patients with stage 2 CKD and obesity was determined (\(p < 0.05\)), and there was a weak correlation between its concentration in the blood and body mass index. A significant average negative correlation between resistin and GFR was detected. Increased serum resistin level correlates with increased TNF-α. In patients of both groups, the level of resistin and LDL increases simultaneously, and the correlation between them increases as CKD progresses. Similar changes are observed with respect to increasing concentrations of resistin and endothelin-1. Thus, an increase of resistin level in the blood in patients with the early stages of CKD initiates a number of pathological changes, such as systemic inflammation, hyperlipidemia and endothelial dysfunction.

Keywords

chronic kidney disease, resistin, tumor necrosis factor-alpha, endothelin-1, total cholesterol, low-density lipoproteins
Introduction

The researches of (Carney 2020) demonstrated that kidney disease has a significant impact on the health of people around the world as a direct cause of global morbidity. Chronic kidney disease (CKD) is an important factor in mortality from non-communicable diseases. The investigations by (Cockwell and Fisher 2020) suggested that all stages of CKD are associated with an increased risk of cardiovascular disease and reduced quality of life. According to data researchers (Fraser and Roderick 2019) the overall prevalence of CKD in 2017 ranged from 8.5 to 9.8%, averaging 9.1%. Although, according to the results of research by Xie et al. (2018) in China, this index was 10.8%. According to data researchers (Hill et al. 2016) depending on the stage of CKD, according to Hill et al. (2016), stage 1 was diagnosed in 3.5%, stage 2 in 3.2% and stage 3 in 7.6%, while stages 4 and 5 took place in 0.4 and 0.1% of the patients respectively. The investigations by (Eckardt et al. 2013) suggested that often in the early stages CKD is asymptomatic, which leads to its untimely diagnosis and progression.

According to some studies (Gu et al. 2013), obesity and high body mass index also contribute to the increase in the prevalence and severity of CKD, and their combination is observed in 3.1% patients with CKD. Currently, some researchers (Allan et al. 2019) recommend the introduction of a new nosological unit – obesity-related glomerulopathy (obesity related nephropathy), which is beginning to be recognized in therapeutic and pediatric nephrology. According to research by Kang et al. (2015), an increase of the visceral fat area, estimated by bioimpedance method, in a population of more than 20 thousand patients older than 18 years, leads to an increase in the incidence of CKD from 6.9 to 13.9%.

In the early 1990s, large-scale and case studies attempted to create a relationship between hyperlipidemia and CKD, and after 10 years of observation, it was shown that the risk of proteinuria increased in patients of both genders with CKD and hypercholesterolemia, low level of high-density lipoprotein (HDL) and high level of low-density lipoprotein (LDL). This suggested a hypothesis of a causal relation between lipid accumulation and the development and progression of CKD (Parmar et al. 2014). According to some studies (Csaba et al. 2016) renal damage and their structural and functional changes in obesity are associated with high metabolic activity of adipose tissue, especially visceral, due to the synthesis of adipocytokines, which have pro-inflammatory, endocrine and paracrine effects.

Resistin is one of such adipocytokines, many research findings have shown the role of which in the development of renal damage is currently being studied (Zhang et al. 2015). The investigations by (Marouga et al. 2016) suggested that resistin may be a risk factor for CKD progression. It is a cysteine-rich protein with a molecular weight of 12.5 KD, which is secreted mainly by adipocytes, although it can be secreted by monocytes, macrophages, bone marrow cells and cardiomyocytes. According to data researchers (Menzaghi et al. 2012) resistin is also a marker of renal clearance like β2-macroglobulin, and its level should increase with decreasing of GFR. Some studies (Chang et al. 2019) have shown that the risk of glomerular changes increases with hyperresistinemia. In addition, according to data researchers (Dan et al. 2014), resistin activates endothelial function, causing inflammatory reactions of the vascular wall. At the same time, a clear consensus on the role of resistin in the development of endothelial dysfunction, lipid storage disease and inflammation in patients with early stages of CKD has not been established.

The purpose of the work: to study changes of resistin level in the blood in patients with early stages of chronic kidney disease, its relation to the level of endothelin, markers of lipid metabolism and inflammation.

Materials and methods

There were 158 patients with chronic kidney disease examined (67 women and 91 men), who were hospitalized in the department of arterial hypertension of Communal non-commercial enterprise “Ivano-Frankivsk Regional Clinical Cardiological Centre of Ivano-Frankivsk Regional Council”, urology and cardiology department of Communal non-commercial enterprise “Central City Clinical Hospital of Ivano-Frankivsk City Council” in Ivano-Frankivsk (Ukraine). The average age of the examined patients was 55.36 ± 2.02 years in women and 47.45 ± 2.66 years in men.

Body mass index was calculated by Kettle formula (kg / m2): BMI = body weight, kg / height, m2. The stage 1 of CKD was diagnosed in 70 patients (31 women, 39 men) with the average age 46.43 ± 3.77 years, and the stage 2 was in 88 patients (36 women, 52 men) with the average age 53.07±2.61 years. Patients were divided into 2 groups: I group (70) – patients with stage 1 CKD and obesity, II group (88) – patients with stage 2 CKD and obesity. The control group consisted of 10 healthy individuals (3 women and 7 men), whose average age was 36.7 ± 8.6 years.

The reasons for the incidence of CKD are as follows: infections of the upper urinary system were in 11.8%, urolithiasis – 19.89%, glomerulonephritis with symptomatic renoparenchymal hypertension – 15.76%, abnormalities in the development of urogenital system – 6, 9%, essential arterial hypertension – 29.1%, coronary heart disease with heart failure – 18.89% patients. The duration of CKD was on average 7.1 years. Exclusion criteria were diabetes hypohalamic and endocrine obesity, acute myocardial infarction, stages 3–4 by NYHA congestive heart failure, hepatic failure, stages 3–4-5 CKD.

General clinical examinations, such as determininthe of the waist circumference (WC), hip circumference (HC) and their ratio was conducted for all patients. WC / HC indicators of abdominal obesity were considered to be > 0.85 in women and > 0.9 in men. The glomerular filtration rate was calculated according to the CKD-EPI formu-
la based on creatinine, cystatin C and their combination (CKD-EPIcysC / cr) (ml / min / 1.73 m²) using a calculator of the US National Renal Fund (http://www.kidney.org/professionals/kdqi/gfr_calculator.cfm). Serum cystatin C levels (0.79–2.15 mg / l in healthy individuals) were measured by enzyme-linked immunosorbent assay using Human Cystatin C ELISA kit (Czech Republic) on STAT FAX analyzer (No. 7898). The resistin level (ng / ml) was determined by sandwich enzyme-linked immunosorbent assay in serum after 14 hours after the last meal furnished using Medigast ELISA E50 Resistin kit (Germany) on STAT FAX analyzer (No. 7898). The concentration of tumor necrosis factor-alpha (TNF-α) in serum (0.02–2.3 pg / ml) was determined by solid-phase enzyme-linked immunosorbent assay using Vector BEST kit (Belarus) on the STAT FAX analyzer. The level of endothelin-1 (reference values within 2.5–7.8 pg / ml) in serum was measured by enzyme-linked immunosorbent assay using the Human ET-1 (Endothelin 1) ELISA Kit (USA) on the STAT FAX analyzer. Determination of total cholesterol was performed by colorimetric method using the Liquick Cor – Chol kit (Poland), determination of low-density lipoprotein level was performed by colorimetric method using Cholesterol-LDL SpL kit (Ukraine).

The research protocol was approved by the Ethics Commission of Ivano-Frankivsk National Medical University, protocol No. 97/17 of 19 October 2017. All patients gave informed consent to participate in it. The study was conducted in accordance with the principles of Helsinki Declaration of the World Medical Association “Ethical principles of medical research with human participation as an object of study” No. 900_005 of 01 October 2008. Statistical analysis of the results was performed using the statistical software package Statistica 6.0 using Student’s t-test. Correlation was assessed by Spearman’s rank correlation coefficient. The discrepancy of the results at p < 0.05 was considered statistically significant.

### Results

It is known that resistin is secreted mainly by preadipocytes, to a lesser extent by adipocytes of adipose tissue, as well as macrophages. As might be seen from the data in Table 1, the level of resistin increased significantly: by 1.28 times in group I patients and 1.6 times – group II compared with healthy individuals (p < 0.05). Correlation analysis in patients of both groups did not show a significant relation between resistin and the age of the patients and the WC / HC. However, a weak direct correlation was found between the level of resistin and BMI in both groups (r1 = 0.23, r2 = 0.36).

As CKD in patients with obesity progressed, the dependence of resistin on the parameters characterizing renal function was revealed. In particular, there was a tendency of relation between the level of resistin and cystatin C in patients of group II (r2 = 0.31), while it was absent in the examined patients of group I, as well as a significant average negative correlation between resistin and the level of GFR calculated by formula CKD-EPIcysC / cr, in both groups (r1 = -0.53 and r2 = -0.65, p < 0.05). There was also revealed a significant correlation between resistin and ESR (r1 = 0.31, r2 = 0.45, t = 2.26 (p < 0.05) in patients of group II, which may indirectly indicate resistin proinflammatory activity. Our data are consistent with the results of studies by Mostafazadeh et al. (2018), which proved the influence of resistin on the processes of renal glomerular remodeling under the circumstances of inflammatory process.

According to data researchers (Kawamura et al. 2010) resistin also mediates the production of other inflammatory cytokines, as another source of hormone synthesis in humans are cells from bone marrow and inflammation. The level of TNF-α increased by 3.6 times in patients of group I and 5.8 times in patients of group II in comparison with the healthy (p < 0.001). We found that the level of resistin in the serum significantly correlates with TNF-α in both groups (r1 = 0.53, r2 = 0.56, p < 0.01), and in patients of group II it was 1.6 times higher than in group I patients (p < 0.001). We found that the level of resistin in the serum significantly correlates with TNF-α in both groups (r1 = 0.53, r2 = 0.58, t = 3.14 (p < 0.01), which is confirmed by the data of Mills et al. (2013), who proved a direct correlation of resistin levels with markers of inflammation, in particular with C-reactive protein and interleukin-6 in patients with CKD.

### Table 1. Characteristics of laboratory parameters in patients with stage 1 and 2 CKD and obesity.

| Parameters | Healthy, n = 10 | Group I, n = 70 | Group II, n = 88 |
|------------|----------------|----------------|-----------------|
| Age, years | 36.7±8.6       | 46.4±3.77      | 53.0±2.61       |
| BMI, kg/m² | 21.4±0.39      | 34.15±1.1      | 35.59±0.82      |
| WC/HC, y.o | 0.71±0.02      | 0.88±0.03*     | 0.93±0.03*      |
| Cystatin C, mg/l | 0.78±0.02     | 1.43±0.13*     | 1.79±0.13*      |
| GFR, ml/min/1.73 m² | 103.3±1.27    | 98.0±2.76      | 64.5±2.07*      |
| ESR, mm/hour | 8.7±0.74      | 18.9±1.36*     | 22.1±1.26*      |
| Resistin, ng/ml | 5.99±0.44     | 7.15±0.22*     | 9.13±0.44*°     |
| TNF-α, pg/ml | 0.73±0.15      | 2.66±0.29*°    | 4.27±0.57°      |
| General cholesterol, mmol/l | 4.24±0.18    | 5.1±0.23       | 6.22±0.36°      |
| LDL, mmol/l | 12.1±0.14      | 2.69±0.19      | 3.89±0.21°      |
| Endothelin, mm/lan | 3.4±0.29   | 5.87±0.48*     | 9.04±0.38°      |

* – significant when compared with healthy individuals;
° – significant when compared with group I and II are compared.

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consistent with the data obtained by Izquierdo-Lahuerta et al. (2016), which showed a negative effect on renal dyslipidemia, accumulation lipids and changes in circulating adipokines, which deepens changes in lipid metabolism, promotes lipid deposition in the mesangial cells of the kidneys and increases insulin resistance.

Endothelin-1, as a marker of endothelial dysfunction, is a powerful vasoconstrictr secreted by endothelial cells and an important regulator of renal function. Its level progressively increased in both groups as GFR decreased and body weight increased by 1.73 and 1.54 times in patients of groups I and II, respectively as compared with the healthy \((p_{1,2} < 0.001)\). The level of endothelin-1 was also significantly correlated with the concentration of resistin in blood serum in both groups \((r_1 = 0.58, p_1 < 0.05, r_2 = 0.71, p_2 < 0.05)\). Our data are also to some extent consistent with the results of research by Samsamshariat et al. (2019), who studied this problem, proved that resistin increases the expression of vasoconstrictor ET-1, which is likely to contribute to endothelial dysfunction.

**Discussion**

Resistin is a cysteine-rich protein secreted mainly by adipocytes, as well as monocytes and macrophages. According to the literature, and according to data researchers (Samsamshariat et al. 2019), laboratory animals and people with obesity have elevated levels of circulating resistin. The investigations by (Zheng et al. 2018) suggested that human genetic studies have suggested that polymorphism in the promoter region of the resistin gene may affect the binding of transcription factor at the level of the messenger ribonucleic acid (mRNA) and may be associated with glucose intolerance in obese people. As a result, it was shown that the level of resistin is affected by BMI. Researches by Hutcheson et al. (2015) proved that if resistin is mainly excreted by the kidneys, as in the case of β2-microglobulin, then the level of resistin should increase as GFR decreases, which is consistent with our data, according to which with the progression of CKD its concentration consistently increased by 27.9% and 63.3% compared to the healthy.

In humans, resistin is mostly expressed by inflammatory cells (mostly macrophages), and activation of the inflammatory cascade enhances resistin expression. Overweight increases the production of TNF-α by adipocytes, which is also a proinflammatory cytokine, and its level increases proportionally to the increase in BMI and correlates with other adipokines, in particular – with resistin. In vitro studies (Jiayu et al. 2019) have shown the expression of mRNA resistin in peripheral blood monocytes with elevated levels after stimulation with interleukin-1–6 and tumor necrosis factor-α, as well as lipopolysaccharides. Plasma resistin levels have also been shown to correlate with markers of inflammation and promote coronary atherosclerosis in humans regardless of TNF-α and CRP levels. Our results are consistent with data from Aghhari et al. (2018), who demonstrated the effect of resistin on the initiation of inflammatory reactions, endothelial damage, vascular smooth muscle cell remodeling, and atherogenesis.

The role of dyslipidemia in CKD development is still being clarified. Recent researches (Li et al. 2020) have shown that circulating in the blood, abnormal lipids are deposited in almost all cell types – from mesangial to podocytes and proximal tubular epithelial. According to Kuma and Uchino (2018), an increase in total cholesterol and high LDL levels are associated with decreased renal function, as evidenced in our study, which were increased, respectively, by 20.3% and 46.7%, and also by 23.4% and 78.4%, respectively, in stages 1 and 2 of CKD.

In vitro, according to data researchers (Weil et al. 2011), it has also been shown that resistin is involved in the activation of endothelin-1 synthesis by endothelial cells, and as a proinflammatory factor, promotes the development of endothelial dysfunction. In addition, the investigations by (Makni et al. 2013), resistin impairs endothelial function by reducing endothelial NO-synthetase expression and nitric oxide levels. Thus, the elevated levels of endothelin-1 found by us indicate a deepening of vascular changes and probably a progressive decrease in glomerular filtration in CKD.

**Conclusion**

Thus, CKD is a condition of chronic inflammation even with a weak and moderate level of renal dysfunction. We found changes in the level of resistin and its possible role in the development of low-intensity inflammation, dyslipidemia, endothelial dysfunction and decreased glomerular filtration rate, which can lead to increased glomerular barrier permeability, induction of renal tubular cell apoptosis and decreased renal function. The obtained data require further research and development of ways to correct the level of this adipokine.

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