

Adropin and irisin levels in relation to nutrition, body composition, and insulin resistance in patients with end-stage renal disease on chronic hemodialysis and peritoneal dialysis

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KEY WORDS

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ABSTRACT

INTRODUCTION Newly discovered myokines, adropin, and irisin, are regulators of energy homeostasis and metabolism in humans. In end-stage renal disease (ESRD), the significance and role of irisin and adropin as metabolism regulators are still unclear.

OBJECTIVES The aim of this study was to evaluate serum adropin and irisin levels and establish their relation to insulin resistance, nutritional status, and hydration status in patients on chronic hemodialysis (HD) and on peritoneal dialysis (PD).

PATIENTS AND METHODS The study consisted of 71 subjects, including 48 patients (18 women, 30 men; median age, 56.5 years; range, 26–84 years) either on HD ($n = 41$) or PD ($n = 7$) and 36 healthy controls matched for age and sex. We measured the serum levels of adropin, irisin, creatinine, albumin, glucose, and insulin, as well as the plasma levels of lipids. The bioimpedance method was used to evaluate the body composition and overhydration in patients with ESRD.

RESULTS Irisin levels were significantly lower in patients with ESRD compared with controls, but there were no differences in adropin levels between both study groups. Adropin levels were inversely correlated with body mass, lean tissue mass, total, intracellular, and extracellular water, and albumin concentrations in patients with ESRD. Irisin levels were positively correlated with glucose levels and homeostasis model assessment of insulin resistance. No significant correlations were observed between adropin and irisin concentrations and overhydration.

CONCLUSIONS Adropin may be considered as a new marker of nutritional status in patients with ESRD. The significance and cause of low irisin levels characteristic for these patients are still unclear. Adropin and irisin should be further investigated as possible markers of cachexia and insulin resistance in patients with ESRD.

INTRODUCTION End-stage renal disease (ESRD) is unequivocally linked to multiple hormonal and metabolic disturbances. Newly discovered tissue hormones, especially myokines and adipokines, have been the subject of numerous recent studies on insulin resistance (IR) and nutritional status in different groups of patients. IR is a nontraditional risk factor involved in cardiovascular disease (CVD) development, and it frequently contributes

to renal failure.¹ Cardiovascular mortality is very high in patients with ESRD, especially in those on chronic hemodialysis (HD).² Adipokines and myokines may be considered as hypothetical links between CVD and the development of IR.

Adropin is a newly discovered regulator of carbohydrate and lipid metabolism, as well as energy expenditure. This bioactive protein contains 76 amino acids chain and has 4499.9 Da of

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molecular weight.³ It was first isolated in mice in 2008 by Kumar et al.⁴ Adropin is a highly conserved polypeptide, which suggests that it has a significant biological role.⁵ So far adropin has been isolated from the liver, muscle, intestine, kidney, heart, pancreas, brain, umbilical vein, and salivary glands.^{3,4,6-8} This secreted peptide was encoded by the energy homeostasis associated (Enho) gene.⁴ Its secretion is regulated by dietary sugar and fat intake.⁴ Adropin causes weight loss and improves glucose tolerance and hepatic lipid metabolism.^{3,4,8}

The effect of adropin on carbohydrate metabolism probably depends on the activation of pyruvate dehydrogenase, which results in the increase of glucose utilization in skeletal muscles. It enhances glucose oxidation and muscle insulin signaling pathways.⁹ Previous studies also suggested that adropin is required for the prevention of obesity-associated IR.^{3,4} Decreased adropin concentrations were described in IR, impaired glucose metabolism and type 2 diabetes, and obesity.^{7,8}

Irisin is a 112 amino acid polypeptide hormone, cleaved from *fibronectin type III domain 5* (FNDC5). Irisin, similarly to adropin, is a well-preserved protein in mammals. This myokine and adipokine was first isolated by Böström et al.¹⁰ Irisin triggers the conversion of white fat to brown-like fat, increases insulin sensitivity, and decreases visceral fat.^{10,11} The available data regarding the effect of long-term exercise training on irisin levels are inconsistent.^{12,13} Yet, weight loss has been described as a factor that decreases irisin levels.^{13,14} Recent data have indicated a negative correlation of irisin with liver fat content, but a positive correlation with muscle mass. Irisin probably reflects human adiposity; however, there is controversy in the association between adipose tissue content and irisin levels.¹⁵ Irisin muscle/adipose tissue secretion index hypothetically depends on the pathophysiological condition of patients.¹⁵ Irisin levels vary in different metabolic states and diseases, such as in thyroid disease, which is linked to muscle damage.^{16,17} In obese patients, irisin levels are adaptively increased.^{13,18} Lower irisin concentrations were observed in diabetic patients.^{18,19}

Irisin is likely not eliminated by the kidneys.²⁰ In a study by Yang et al,²¹ high irisin levels in serum were associated with reduced risk of chronic kidney disease (CKD). Wen et al²² found that plasma irisin levels were significantly decreased in these patients. Glomerular filtration rate was independently related to irisin levels.²⁰ Liu et al²³ established an independent association between irisin levels and glomerular filtration rate in diabetic patients. A large study, conducted by Ebert et al,²⁰ involving 532 patients with CKD, proved that serum irisin levels decline with progression of CKD (stages 1–5). Finally, reduced irisin secretion in these patients was also attributed to an increase in uremic toxins (eg, indoxyl sulfate) that caused a decrease in the levels of irisin precursor, FNDC5, produced in skeletal muscle cells.²²

Currently, there are no data in the literature demonstrating the effect of CKD on adropin levels. Similarly, data on irisin and ESRD are also limited.²⁰⁻²² We hypothesized that adropin and irisin concentrations may be associated with body composition, overhydration, and IR markers in patients with ESRD receiving renal replacement therapy (RRT). Therefore, the aim of our study was to answer the question of whether adropin and irisin levels might be useful markers of hydration, IR, and nutritional status in this patient group.

PATIENTS AND METHODS **Patients** The study included 48 patients with ESRD receiving RRT (18 women, 30 men; median age, 56.5 years; range, 26–84 years) and 36 healthy controls matched for age and sex. Of patients on RRT, 41 were treated with HD and 7 were treated with PD at the center where they were recruited to the study. The exclusion criteria were as follows: diabetes or glucose intolerance, active malignant neoplasm, autoimmune disease, active inflammatory disease, and advanced hepatic disease. The Ethics Committee of the Poznan University of Medical Sciences approved the study protocol. All participants signed an informed consent form.

Blood measurements In HD patients, fasting blood samples were collected before a midweek HD session and in PD patients, before PD session. Peripheral venous blood samples were taken from an arteriovenous fistula, venous catheter, or antecubital vein of patients. The samples were clotted and stored at –80°C until analysis.

Serum adropin levels were measured twice prior to an HD or PD session, using an enzyme-linked immunosorbent assay, following which the results were averaged. The Human Adropin (ENHO) Elisa Kit (Cusabio Biotech Co, Wuhan, China) was used. The sensitivity of the assay was below 0.39 pg/ml. Serum irisin levels were determined twice using the AdipoGen ELISA Kit prior to an HD or PD session, following which the results were averaged. The lowest concentration of irisin that could be detected by this assay was 1 ng/ml.

The levels of creatinine, albumin, glucose, and fasting serum insulin were measured also prior to an HD or PD session. Serum lipid markers including total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured at the same time as well. Homeostasis model assessment was used for the assessment of IR and the calculation of the homeostasis model assessment of insulin resistance (HOMA-IR).²⁴ In the control group, serum creatinine, glucose, insulin, lipid markers, albumin, adropin, and irisin levels were also measured and the HOMA-IR was calculated. The measurements were performed in the accredited and quality-controlled Central Laboratory of the Heliodor Świącicki University Hospital in Poznań, Poland.

TABLE 1 Comparison of clinical parameters between patients with end-stage renal disease and controls

Parameters	Patients (n = 48)	Controls (n = 36)	P value
age, y	56.5 (40.00–66.50)	54 (48.00–59.00)	0.55
body mass, kg	69.60 (62.65–79.80)	79.825 (67.97–90.00)	0.02
height, m	1.68 (1.63–1.75)	1.75 (1.64–1.80)	0.07
BMI, kg/m ²	23.71 (21.72–27.79)	26.49 (24.47–29.05)	0.03
creatinine, mg/dl	7.61 (6.72–10.94)	0.785 (0.66–0.93)	0.000001
albumin, g/dl	4.21 (4.09–4.64)	4.28 (4.15–4.38)	0.08
glucose, mg/dl	66.50 (45.50–89.00)	94.00 (89.00–97.00)	0.0001
insulin, mIU/ml	9.70 (5.50–16.30)	10.00 (6.70–14.60)	0.98
HOMA-IR	1.41 (0.78–2.66)	2.285 (1.30–3.40)	0.08
TC, mg/dl	195.50 (141.00–214.00)	203.50 (182.00–226.00)	0.01
HDL cholesterol, mg/dl	47.00 (33.00–54.00)	45.00 (36.00–59.00)	0.33
LDL cholesterol, mg/dl	118.30 (76.60–133.80)	133.00 (113.00–152.00)	0.33
TG, mg/dl	146.50 (103.00–172.00)	101.50 (84.00–171.00)	0.11

A *P* value of less than 0.05 was considered significant.

Data are expressed as median (interquartile range). The Mann–Whitney test was used to determine the differences between the groups.

Conversion factors to SI units are as follows: for creatinine, 0.00884; albumin, 10; glucose, 0.05551; insulin, 1; TC and HDL cholesterol, 0.02586; TG, 0.0114.

Abbreviations: BMI, body mass index; HDL, high-density lipoproteins; HOMA-IR, insulin resistance index with use homeostasis model assessment; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol

Anthropometry and body composition measurements

Weight was measured to the nearest 10 g, using a digital scale. Height was measured to the nearest 5 mm, using a wall-mounted stadiometer. Body mass index (BMI) was calculated using height and weight (kg/m²).

Body composition measurement by bioelectrical impedance

Body composition measurements with the use of bioimpedance (Body Composition Monitor, BCM, Fresenius Medical Care, Deutschland GmbH, Bad Homburg v.d.H., Germany) were selectively conducted in 46 patients with ESRD only and not in controls. The BCM analysis has been specifically designed for patients with renal failure. All measured parameters were validated against the gold standard reference methods from various studies involving more than 500 patients and healthy controls. The measured parameters were as follows: fat tissue mass (kg); lean tissue mass (kg); total body water (l), intracellular water (l); extracellular water (l), overhydration (l); normohydration weight (kg), and distribution volume of urea (V_{urea}, l). A single trained and experienced investigator performed all the measurements.

Statistical analysis All statistical analyses were performed using a data analysis software system, STATISTICA 2014, v 12 (StatSoft, Inc., Tulsa, Oklahoma, United States). To test whether the underlying distribution was normal, the Shapiro–Wilk test was used. Results were expressed as median and interquartile range. A *P* value of less than 0.05 was considered as statistically

significant. In order to determine the differences in adropin and irisin levels between patients with ESRD and controls, the Mann–Whitney test was used. A possible association among the measured parameters was assessed using the Spearman’s rank correlation coefficient.

RESULTS Clinical characteristics of participants

The clinical characteristics and biochemical data of control subjects and ESRD patients are summarized in **TABLE 1**. Notably, in comparison with controls, lower levels of glucose were observed in patients with ESRD. Significant differences were observed between the control and patient group for body mass, body mass index (BMI), and creatinine, glucose, and total cholesterol levels.

Adropin and irisin levels There were no differences in the levels of adropin between controls and patients with ESRD (3.92 ng/ml vs 4.21 ng/ml, non-significant). The levels of irisin were significantly lower in patients with ESRD compared with controls (4.57 µg/ml vs 7.90 µg/ml; *P* = 0.000001) (**TABLE 2**).

Anthropometric studies Negative correlations were observed between the level of adropin and body mass (*r* = −0.509; *P* = 0.0002), BMI (*r* = −0.326; *P* = 0.02), and normohydration weight (*r* = −0.524; *P* = 0.0001) in patients with ESRD. Adropin was positively correlated with age (*r* = 0.299; *P* = 0.04) (**TABLE 3**). Irisin levels were not correlated with anthropometric measurements or age. Adropin and irisin concentrations were negatively correlated with body mass in controls (*r* =

TABLE 2 Adropin and irisin levels in patients with end-stage renal disease and controls

Parameters	Patients (n = 48)	Controls (n = 36)	P value
adropin, ng/ml	4.21 (3.54–5.02)	3.92 (3.15–5.04)	0.5
irisin, µg/ml	4.57 (3.48–6.38)	7.90 (6.54–9.45)	0.000001

A *P* value of less than 0.05 was considered significant.

Data are presented as median (interquartile range). The Mann–Whitney test was used to determine the differences between groups.

TABLE 3 Correlation coefficients for irisin and adropin in comparison to anthropometric and body composition measurements in patients with end-stage renal disease and controls

Parameters	Patients (n = 48)		Controls (n = 36)	
	adropin	irisin	adropin	irisin
age	$r = 0.299$ $P = 0.04$	$r = -0.122$ $P = 0.41$	$r = 0.062$ $P = 0.74$	$r = 0.251$ $P = 0.16$
body mass	$r = -0.509$ $P = 0.0002$	$r = -0.003$ $P = 0.99$	$r = -0.386$ $P = 0.04^a$	$r = -0.510$ $P = 0.004$
BMI	$r = -0.326$ $P = 0.02$	$r = -0.040$ $P = 0.79$	$r = -0.249$ $P = 0.2$	$r = -0.329$ $P = 0.08$
NH weight	$r = -0.525$ $P = 0.0001^a$	$r = -0.058$ $P = 0.70$	NA	NA
BCM	$r = -0.646$ $P = 0.000001$	$r = -0.122$ $P = 0.43$	NA	NA
LTM	$r = -0.671$ $P = 0.000001$	$r = -0.144$ $P = 0.35$	NA	NA
LTI	$r = -0.529$ $P = 0.0001$	$r = -0.106$ $P = 0.49$	NA	NA
TBW	$r = -0.661$ $P = 0.000001$	$r = -0.159$ $P = 0.29$	NA	NA
ICW	$r = -0.735$ $P = 0.000001$	$r = -0.155$ $P = 0.31$	NA	NA
ECW	$r = -0.511$ $P = 0.0002$	$r = -0.173$ $P = 0.26$	NA	NA
V urea	$r = -0.679$ $P = 0.000001$	$r = -0.172$ $P = 0.26$	NA	NA
OH	$r = -0.086$ $P = 0.57$	$r = -0.129$ $P = 0.4$	NA	NA
OH/ECW	$r = 0.165$ $P = 0.27$	$r = -0.096$ $P = 0.53$	NA	NA

A *P* value of less than 0.05 was considered significant.

Abbreviations: BCM, body composition measurement by bioelectrical impedance; ECW, extracellular water; ICW, intracellular water; LTI, lean tissue index; LTM, lean tissue mass; NA, not available; NH, normohydration; OH, overhydration; TBW, total body water; V urea, distribution volume of urea; others, see [TABLE 1](#)

-0.386 , $P = 0.04$; $r = -0.510$, $P = 0.004$). No correlation between age and level of these 2 myokines were found in controls ([TABLE 3](#)).

Body composition monitoring In the ESRD group, inverse correlations were found between the level of adropin and V urea ($r = -0.679$, $P = 0.000001$), total body water ($r = -0.661$, $P = 0.000001$), intracellular water ($r = -0.735$, $P = 0.000001$), extracellular water ($r = 0.511$, $P = 0.0002$), lean tissue

mass ($r = -0.671$, $P = 0.000001$), lean tissue index ($r = -0.529$, $P = 0.0001$), and body cellular mass ($r = -0.646$, $P = 0.000001$). No correlations were found between irisin concentrations and body cellular mass measurements. Furthermore, no significant relationships were observed between adropin or irisin levels and overhydration ([TABLES 3](#) and [4](#)).

Metabolic and nutrition parameters Adropin was negatively correlated with a laboratory parameter of nutritional status, albumin ($r = -0.387$, $P = 0.007$) in patients with ESRD. There were no significant correlations between adropin and glucose or insulin levels and HOMA-IR both in renal patients and controls. Contrary to the patient group, adropin was positively correlated with albumin in controls ($r = 0.355$, $P = 0.046$).

Irisin concentrations were positively correlated with glucose levels ($r = 0.644$, $P = 0.000001$) and HOMA-IR ($r = 0.455$, $P = 0.001$) in patients with ESRD. However, in contrast to renal patients, negative correlations between irisin and HOMA-IR ($r = -0.499$, $P = 0.008$) and insulin ($r = -0.492$, $P = 0.009$) were found in the control group. No correlations between irisin and adropin levels and serum lipid markers were observed in renal patients. In controls, significant correlations were found between adropin and triglycerides ($r = -0.479$, $P = 0.005$) and HDL cholesterol ($r = 0.528$, $P = 0.002$) ([TABLE 5](#)).

DISCUSSION Malnutrition is often observed in patients with ESRD. The prevalence of malnutrition in HD patients is estimated at about 30%.²⁵ Malnutrition and wasting is related to low skeletal muscle mass and reduced irisin levels.²⁶ HD patients are characterized by lower muscle mass, muscle atrophy along with intramuscular lipid accumulation, and a lower muscle mass/total body mass ratio.²⁷ Lower irisin levels were described in anorexia nervosa, and higher irisin levels are characteristic for obese patients.²⁶ A decrease in the irisin level was observed in patients losing weight after bariatric surgery.¹³ Nonetheless, irisin levels did not change during starvation in a study on rats.²⁸ Irisin reduction has protective effects against energy loss by preserving energy through decreasing of browning of white adipocytes.²⁹ It is questionable whether irisin is really an “exercise hormone” and whether chronic exercises increase irisin levels.¹⁵ We expected lower irisin levels in patients with ESRD because of malnutrition–inflammation–atherosclerosis syndrome in patients with ESRD, but we did not find any correlation between irisin concentrations, anthropometric and body composition measurements, or levels of albumin and triglycerides in patients with ESRD. These patients were characterized by a significantly lower body mass and BMI in comparison with controls. Although irisin concentrations were negatively correlated with body mass in controls, lower body mass in patients with ESRD did not seem to be the reason for lower irisin levels

TABLE 4 Body composition results with the use of bioimpedance in patients with end-stage renal disease

Variables	Patients (n = 48)
NH weight, kg	76.2 (61.30–78.40)
BCM, kg	20.8 (15.60–24.50)
LTM, kg	39.6 (29.20–43.20)
LTI, kg/m ²	13.1 (11.60–14.20)
TBW, l	38.0 (30.00–40.00)
ICW, l	20.1 (15.60–20.70)
ECW, l	18.3 (14.00–19.10)
V urea, l	36.9 (28.40–37.30)
OH, l	2.1 (0.20–2.90)
OH/ECW	0.073 (0.015–0.165)

Data are presented as median (interquartile range).

Abbreviations: see [TABLE 3](#)

TABLE 5 Correlation coefficients for irisin and adropin in comparison to serum biochemical parameters in patients with end-stage renal disease and controls

Parameters	Patients (n = 48)		Controls (n = 36)	
	adropin	irisin	adropin	irisin
creatinine	$r = -0.131$ $P = 0.37$	$r = -0.207$ $P = 0.16$	$r = 0.0123$ $P = 0.94$	$r = -0.253$ $P = 0.17$
albumin	$r = -0.387$ $P = 0.007^a$	$r = -0.078$ $P = 0.61$	$r = 0.355$ $P = 0.046^a$	$r = 0.168$ $P = 0.37$
glucose	$r = 0.268$ $P = 0.07$	$r = 0.644$ $P = 0.000001^a$	$r = -0.253$ $P = 0.21$	$r = 0.031$ $P = 0.88$
insulin	$r = -0.203$ $P = 0.17$	$r = 0.170$ $P = 0.25$	$r = -0.167$ $P = 0.41$	$r = -0.499$ $P = 0.008$
HOMA-IR	$r = -0.059$ $P = 0.69$	$r = 0.455$ $P = 0.001$	$r = -0.166$ $P = 0.42$	$r = -0.492$ $P = 0.009$
TC	$r = 0.042$ $P = 0.78$	$r = 0.140$ $P = 0.36$	$r = -0.104$ $P = 0.57$	$r = 0.235$ $P = 0.20$
TG	$r = -0.169$ $P = 0.26$	$r = 0.268$ $P = 0.08$	$r = -0.479$ $P = 0.005$	$r = 0.026$ $P = 0.89$
HDL cholesterol	$r = 0.239$ $P = 0.11$	$r = 0.181$ $P = 0.23$	$r = 0.528$ $P = 0.002$	$r = 0.237$ $P = 0.2$
LDL cholesterol	$r = 0.031$ $P = 0.84$	$r = -0.010$ $P = 0.5$	$r = -0.184$ $P = 0.32$	$r = 0.147$ $P = 0.44$

A P value of less than 0.05 was considered significant.

Abbreviations: see [TABLES 1 and 3](#)

in this group of patients. To sum up, the cause of low irisin levels and its consequence in this patient group requires further studies.

Adropin, as a factor that governs glucose and lipid homeostasis, is a potential nutritional parameter. Liver Enho expression is regulated by nutrition.⁴ An association between diet and adropin concentration was observed in animal and human studies.^{3,4,30} A rise in adropin levels was described with an increase in fat intake.^{3,4,30} Furthermore, low-carbohydrate diet led to an increase in adropin levels.^{3,30} On the other hand, lower adropin levels were described in obese patients. Contrary to changes seen in irisin, adropin concentrations

increase after gastric bypass surgery in humans.⁸ Adropin deficiency is connected with increased adiposity and IR.³ We expected a variation in adropin concentrations in patients with ESRD because of kidney failure itself as well as concomitant changes in adiposity and body composition related to the disease. However, adropin levels did not differ between patients with ESRD and controls in our study. On the other hand, we observed significant associations between adropin and nutritional parameters in the ESRD group. There was an inverse correlation between adropin and body mass, BMI, and albumin in patients with ESRD. Similarly, a negative association between adropin

and body mass was observed in controls. There was also a positive relationship between adropin and albumin levels in controls. A negative correlation between adropin levels and BMI was described previously.^{8,31} Lower adropin levels were also found in obese children.³² In contrast, one study so far has shown a positive correlation between plasma adropin levels and BMI in patients with heart failure.³³ In ESRD patients, an “obesity paradox” or “reverse epidemiology” has been described. A higher BMI is paradoxically linked to better prognosis and survival.³⁴ Whether malnutrition with the often coexisting visceral obesity in HD patients interferes with adropin levels still remains unclear.

To our knowledge, this is the first study that has described the relationship between serum adropin concentrations and body composition in humans. So far, similar studies have been conducted only in mice, with the use of a Minispec Live Mice Analyzer (Bruker Mice Minispec NMR Analyzer; Bruker Optics, Inc.; Billerica, Massachusetts, United States).^{4,9} Adropin knockout mice were characterized by diminished motor activity and increased body weight, which was solely attributed to an increase in fat mass.^{4,35} Furthermore, adropin deficiency resulted in an increase of adipose tissue mass and dyslipidemia in mice.³ Adropin disturbances might have affected body weight and body composition. In our study, lean body mass³⁶ was inversely correlated with adropin levels. Thus, in ESRD patients, tissues other than muscles potentially become the primary sources of adropin instead. Perhaps cachexia and concomitant muscular atrophy in patients with ESRD contributes to the altered adropin level.

Adropin was related to total body water, extracellular water, and intracellular water, but not overhydration or overhydration / extracellular water in patients with ESRD. It is a well-known fact that water constitutes 70% of muscle composition. Our results indicate that adropin is not a marker of overhydration in patients with ESRD. Perhaps establishing this relationship in controls is needed before it can be explored in disease processes such as ESRD. In humans, there are no data comparing body composition measurements and adropin. Such data, acquired with the use of a different tool (Minispec Live Mice Analyzer), is available only in mice.^{3,9}

Irisin is classified as an adipo-myokine.³⁷ Just like in the previous study by Yang et al,¹⁹ we did not find any significant correlation between irisin levels and body composition measurements. In fact, only a few earlier studies have reported a positive correlation between irisin and body mass, BMI, and fat mass.^{13,26,38} Elevated irisin levels, probably in response to hyperglycemia, were also found in obese patients.¹⁴ Serum irisin concentrations declined with weight loss.²⁶ Our results did not support the hypothesis that irisin is a useful indicator of body fat mass, as in this study irisin levels were not related to muscle mass, BMI, or body mass in patients with ESRD.

Yet there was a negative correlation between irisin and body mass in the control group. Our results seem to confirm the theory of “reverse epidemiology” in this patient group.

Impaired glucose metabolism develops under conditions of metabolic stress accompanying ESRD. Almost all patients with ESRD are characterized by abnormal glucose metabolism.^{39,40} Adropin is believed to be a factor in reducing glucose intolerance and IR.^{3,4,41} However, our study does not support this theory. We did not find a relationship between adropin and glucose or insulin levels or HOMA-IR in patients with ESRD or controls. Sesti et al⁴² reported a positive correlation between sensitivity to insulin and adropin levels in patients with glucose intolerance. Lower adropin concentrations in blood were associated with glucose impairment and IR in mice and humans.^{3,8} Similarly, mothers with gestational diabetes were found to have lower adropin levels in blood.⁴¹ Negative correlations between serum adropin levels and fasting insulin levels and HOMA-IR were described in patients with polycystic ovary syndrome.⁴³ However, no differences in adropin levels between patients with cardiac syndrome X with and without IR were observed by Celik et al.⁴⁴ An influence of adropin on insulin but not glucose levels was observed by Goetze et al.⁵ The above data are not consistent with the results of our study.

Irisin was thought to improve glucose metabolism. Decreased irisin levels were found in patients with type 2 diabetes.^{18,19} Choi et al¹⁴⁵ found an inverse correlation between hemoglobin A_{1c} and irisin levels in patients with type 2 diabetes. Sesti et al¹⁴⁶ also found a negative relationship between irisin and insulin sensitivity. We found significant positive correlations between irisin and glucose levels ($r = 0.644$, $P = 0.000001$) and HOMA-IR ($r = 0.455$, $P = 0.001$) in patients with ESRD. In a multivariate analysis by Ebert et al,²⁰ a similar association between the HOMA-IR and irisin was found.²⁰ Furthermore, Moreno et al⁴⁷ found a positive association between circulating irisin levels and HOMA-IR and fasting insulin levels in sedentary patients. Therefore, our results do not support the hypothesis that irisin improves glucose tolerance and IR in patients with ESRD. Low irisin levels also do not seem to be connected with IR in these patients. Unlike in patients with ESRD, we observed negative correlations between irisin levels and IR. It is possible that irisin affects glucose tolerance in healthy individuals and in those with disease processes associated with metabolic impairment.

Some investigators have also noted negative relationships between adropin and cholesterol, very low-density lipoprotein cholesterol, and triglycerides in women with polycystic ovary syndrome.⁴³ In a similar manner, serum adropin levels negatively correlated with triglycerides in patients after myocardial infarction and those with metabolic syndrome after gastric bypass.^{8,31} These findings could be to some extent attributed to the

nature of adropin in inhibition of lipogenesis.⁴ In this study, we did not find associations between adropin and lipids in patients with ESRD, but we found interactions between adropin and triglyceride and HDL cholesterol levels in controls. Regulation of lipid metabolism could be different in ESRD. A small number of enrolled patients could bias the results.

Irisin was independently correlated with total cholesterol and low-density lipoprotein cholesterol levels in a study by Tang et al⁴⁸ and with HDL cholesterol levels in a study by Wen et al.²² In contrast to these previous studies, we did not observe any correlations between the levels of irisin and those of HDL cholesterol or other lipid metabolism parameters either in patients with ESRD or in controls.

The major limitation of this study was a small number of patients, resulting from strict exclusion criteria, which might have overestimated the magnitude of associations. The lack of body cellular mass measurements in controls is another limitation of this study. Further larger studies are needed to explain the role of adropin and irisin in metabolic homeostasis of patients with ESRD.

Conclusions Adropin and irisin may potentially have various metabolic effects in patients with ESRD. Adropin seems to be a reasonable, negative predictor of nutrition in these patients. We found adropin levels to be related to lean tissue mass, while they were not correlated with IR. However, low irisin levels in this patient group were not explained by our study, and further research is needed. Irisin levels positively correlated with IR. The significance of decreased irisin levels in patients with ESRD is unknown. Neither adropin nor irisin appeared to be a marker of overhydration in this patient group. Both adropin and irisin should be interpreted while taking into account patients' individual residual renal function and concurrent disorders. These new polypeptide hormones should be further investigated in a larger population of patients as potential markers of nutritional state and IR in patients with ESRD.

Contribution statement MK was responsible for the overall concept and design of the study, for review of the literature, as well as data analysis and writing of the paper. KH, KS, and AIY were responsible for recruitment of patients. AIY was responsible for preparation of the article. KP was responsible for the execution of the project, data analysis, and writing of the paper. KZ was responsible for the overall concept of the study, execution of the project, data analysis, and writing of the paper.

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Stężenia adropiny i iryzyny w odniesieniu do stanu odżywienia, składu ciała i insulinooporności u pacjentów ze schyłkową niewydolnością nerek leczonych przewlekłe hemodializą lub dializą otrzewnową

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SŁOWA KLUCZOWE

adropina, iryzyna,
hemodializa,
insulinooporność,
schyłkowa
niewydolność nerek

STRESZCZENIE

WPROWADZENIE Nowo odkryte miokiny, adropina i iryzyna, są regulatorami energii i metabolizmu u ludzi. W schyłkowej niewydolności nerek (SNN) znaczenie i rola iryzyny i adropiny jako regulatorów metabolizmu są wciąż niejasne.

CELE Celem badania było określenie stężeń adropiny i iryzyny oraz ustalenie ich związku z insulinoopornością, stanem odżywienia i nawodnienia u pacjentów leczonych przewlekłe hemodializą (HD) bądź dializą otrzewnową (DO).

PACJENCI I METODY Do badania włączono 71 osób: 48 pacjentów (18 kobiet, 30 mężczyzn, mediana wieku 56,5 roku, zakres 26–84) leczonych HD ($n = 41$) lub DO ($n = 7$) oraz 36 zdrowych osób dobranych pod względem płci i wieku. W surowicy krwi oznaczono stężenia adropiny, iryzyny, kreatyniny, albuminy, glukozy i insuliny, a w osoczu stężenie lipidów. Skład ciała i przewodnienie u pacjentów z SNN zostały oszacowane za pomocą bioimpedancji.

WYNIKI Stężenia iryzyny były istotnie niższe u pacjentów z SNN w porównaniu z grupą kontrolną, natomiast w badanych grupach nie zaobserwowano różnicy między stężeniami adropiny. Stężenia adropiny korelowały negatywnie z masą ciała, masą tkanki mięśniowej, całkowitą, wewnątrzkomórkową i zewnątrzkomórkową wodą oraz stężeniem albuminy u pacjentów z SNN. Pozytywną korelację zaobserwowano między stężeniem iryzyny a stężeniem glukozy i wskaźnikiem HOMA-IR (*homeostasis model assessment of insulin resistance*) w grupie chorych z SNN. Nie zaobserwowano istotnych związków między stężeniami adropiny i iryzyny a przewodnieniem.

WNIOSKI Adropina może być rozważana jako nowy marker stanu odżywienia pacjentów z SNN. Przyczyna i znaczenie niskich stężeń iryzyny, charakterystycznych dla tych pacjentów, są nadal niewyjaśnione. Należy prowadzić dalsze badania nad adropiną i iryzyną jako potencjalnymi markerami kacheksji i insulinooporności u pacjentów z SNN.

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