Original Article

Lower serum irisin levels are associated with the increasing mortality of cardiovascular and cerebrovascular diseases in hemodialysis patients

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Background: Irisin is a recently discovered myokine/adipokine and lower levels of irisin were proved to be associated with adverse outcomes of cardiovascular and cerebrovascular diseases (CCVD) in general population. A significant decrease of irisin concentrations were also detected in patients with chronic kidney disease (CKD). In the present study, we investigated whether the serum irisin levels were associated with cardiovascular and cerebrovascular mortality in hemodialysis (HD) patients.

Methods: This retrospective cohort study enrolled 152 HD patients. Kaplan-Meier analysis was used to estimate the cumulative mortality of CCVD. The differences between the survival curves were compared by log-rank test. A multivariable Cox regression analysis was employed to identify the predictors of CCVD related deaths.

Results: Among 152 HD patients, 55 patients died and 18 of them died of CCVD, 97 HD patients survived. Compared with the survival group, patients died of CCVD had significantly lower serum irisin levels [23.6 (2.2, 319.4) *vs.* 45.7 (2.1, 367.8) ng/mL, P<0.05]. The Kaplan-Meier survival curves showed that patients with lower levels of irisin had higher CCVD mortality. The Cox regression analysis indicated lower irisin level as an independent risk factor for CCVD mortality in HD patients but not for all-cause mortality.

Conclusions: Our results provided an association between lower irisin level and CCVD mortality in HD patients. Lower levels of irisin increased the mortality of CCVD in HD patients.

Keywords: Irisin; hemodialysis; cardiovascur disease; cerebrovascular disease; mortality

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Introduction

Irisin is a recently discovered myokine/adipokine composed of 112 amino acid and a product of fibronectin type III domain 5 (FNDC5) cleavage (1). It could drive brown-fat-like conversion of white fat and increase energy expenditure. Studies have proved that irisin was involved in many metabolic diseases such as obesity, type 2 diabetes, nonalcoholic fatty liver disease and polycystic ovary syndrome (PCOS) (2). Additionally, lower irisin levels were also associated with cardiovascular disease (CVD) (3-5) and cerebrovascular disease (6,7), especially with their adverse outcomes in general population. Patients with chronic kidney disease (CKD) have a higher prevalence of cardiovascular and cerebrovascular diseases (CCVD) (8). CVD is the leading cause of deaths in patients with end-stage renal disease (ESRD) (9). Besides, the stroke risk in patients with CKD was also proved to have a graded and independent association with estimated glomerular filtration

rate (eGFR) (10,11). Recently, accumulating evidences have shown that decreasing irisin serum concentrations in parallel with the increasing CKD stage can predict kidney function (12). Furthermore, He and Wen *et al.* also reported that the circulating irisin levels were significantly decreased in CKD and hemodialysis (HD) patients (13,14). The reason why patients with CKD or undergoing renal replacement therapy have lower irisin levels could be attributed to persistent protein energy wasting (PEW) in CKD which is caused by metabolic acidosis, inflammation, increased angiotensin II level, abnormal appetite regulation (15,16) and results in striking loses of muscle proteins and skeletal muscle wasting and atrophy (17). Taken together, we hypothesized that decreased irisin levels may increase the risk of CCVD mortality in HD patients. In this research, we performed a retrospective cohort study with Chinese HD patients. We aimed at investigating the association of serum irisin with CCVD mortality. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-406).

Methods

Subjects

This retrospective cohort study was to investigate the relationship between irisin and CCVD mortality in HD patients. Participants were excluded if: (I) their age is under 18; (II) they had initiated HD for less than 3 months. Inclusive criteria were as follow: (I) age over 18; (II) initiated HD time over three months; (III) agree to participate this study.

From January to May 2014, 170 patients had received HD in our hospital, 152 of them were consecutively enrolled according to inclusive and exclusive criteria and were followed by the end of December 2019. The patients enrolled who had a history of cardiovascular/cerebrovascular diseases were all at stable state. Besides, we compared the irisin levels of patients with and without a history of cardiovascular/cerebrovascular diseases, the result didn't show any statistical significance (data not shown). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of our hospital (No. [2019]130), and individual consent for this retrospective analysis was waived.

Data collection

Demographic and clinical data including age, sex, HD vintage were collected. All the laboratory data such as hemoglobin, serum creatinine, urea nitrogen, uric acid, glucose, phosphorus, calcium, albumin, intact parathyroid hormone (iPTH), lipid profile, ultra-sensitive C reactive protein (usCRP), etc. were collected at baseline. Fractional urea clearance (Kt/V urea) was calculated by Daugirdas formula.

Measurement of serum irisin

Blood samples were collected after fasting for at least 8 hours before HD using vacuum tubes without anticoagulant. Then they were centrifuged and the serum was separated and stored at −80 ℃ until analysis. Serum irisin was measured using enzyme linked immunosorbent assay (ELISA) kits (Phoenix Pharmaceuticals, USA). Inter- and intra-assay coefficients of variation were less than 15% and less than 10%, respectively.

End point event definition

All-cause deaths were defined as the deaths of CCVD, cancer or malignant tumor, infectious diseases or other causes (liver necrosis, malnutrition), CCVD deaths were defined as deaths of coronary heart disease, congestive cardiac failure, cardiac sudden death, cerebro infarction or cerebro hemorrhage.

Statistical analysis

Results were expressed as proportions for categorical variables, means ± standard deviation (SD) for continuous variables with normal distributions, and medians (range) for continuous variables with non-normal distributions. The Student's *t*-test was employed to compare differences between the two groups for normally distributed data, while the Mann-Whitney U test was used for non-normal data. Categorical data were compared using the Chi-square test. Kaplan-Meier methods were used to estimate cumulative mortality of CCVD. The differences between the survival curves were compared by log-rank test. We selected variables that were statistically significant ($P<0.05$) in the comparisons of baseline irisin and other parameters between HD patients CCVD/all-cause death and survival HD patients as covariates for the multivariable analysis (Cox regression analysis) of all-cause mortality or CCVD mortality. Additionally, we confirmed that the covariates we included didn't have multicollinearity. SPSS version

Table 1 Baseline demographic and clinical characteristics in hemodialysis patients

Characteristics	Hemodialysis patients (n=152)
Age (years)	64.2±15.0
Male/female (n)	89/63
HD Vintage (month)	61.7 (15.0, 308.6)
KT/V urea	1.4±0.5
Systolic pressure (mmHg)	144.5±21.3
Hemoglobin (g/L)	111.9±12.4
Serum creatinine (μmol/L)	909.9±244.1
Serum urea (mmol/L)	26.2±5.7
Serum uric acid (μmol/L)	470.7±94.4
Serum calcium (mmol/L)	2.3±0.2
Serum phosphate (mmol/L)	1.9±0.5
Serum albumin (g/L)	41.7±3.57
Serum glucose (mmol/L)	6.7±2.7
Serum usCRP (mg/L)	2.9 (0.1, 87.5)
Serum LDL-C (mmol/L)	2.1±0.7
Serum HDL-C (mmol/L)	0.9±0.3
Serum triglycerides (mmol/L)	1.8 (0.1, 10.2)
Serum total cholesterol (mmol/L)	3.9±1.0
iPTH (pg/mL)	169.5 (10.0, 3,630.0)
Serum irisin (ng/mL)	50.1 (2.1, 367.8)
CCVD history (with/without)	47/105

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; iPTH, intact parathyroid hormone; usCRP, ultra-sensitive C reactive protein; Kt/V urea, fractional urea clearance.

23.0 was used for statistical analysis, all analyses were two-tailed, and a P value <0.05 was defined as the threshold of statistical significance.

Results

Baseline characteristics of subjects

This study consisted of 152 HD patients. The mean of follow-up period was 52.58±20.64 (months). The primary renal diseases were composed of chronic glomerulonephritis (43 patients), diabetic kidney disease (DKD) (30 patients), hypertensive glomerulosclerosis (15 patients), other diseases such as chronic interstitial nephritis and systemic lupus erythematosus (27 patients) and renal diseases with unknown causes (37 patients). Of the 152 patients, 47 had a history of cardiovascular/cerebrovascular diseases and 105 didn't. The baseline demographic and clinical characteristics are shown in *Table 1*. Besides, to confirm the baseline characteristics of patients with high and low levels of irisin didn't have statistical significance which may influence the results, we stratified the patients by the median value of irisin concentrations (50.09 ng/mL) into two groups and compared their baseline characteristics. The result showed that there wasn't any significant difference between the two groups (see *Table 2*).

Comparison of irisin and other parameters between HD patients of all-cause death and survival HD patients

Among all HD patients, 55 patients died and 97 HD patients survived. Compared with the survival group, the dead patients had older age, higher systolic pressure and significantly lower levels of serum creatinine, uric acid, phosphate, albumin, LDL-C, triglycerides and total cholesterol. However, the serum irisin levels in the two groups had no significant difference (see *Table 3*).

Comparison of baseline irisin and other parameters in HD patients died of CCVD and survival HD patients

Of the 152 HD patients, 18 patients died of CCVD and 97 HD patients survived. As shown in *Table 4*, compared to the survival patients, the HD patients died of CCVD had significantly lower levels of serum irisin [23.6 (2.2, 319.4) ng/mL *vs.* 45.7 (2.1, 367.8) ng/mL, P<0.05]. Additionally, there were more female patients in the patients died of CCVD, and they also had older age, lower hemoglobin, serum creatinine, phosphate and higher systolic pressure. Not surprisingly, patients who had a history of CCVD also presented higher risk of CCVD death. However, there was no significance in HD vintage, KT/V urea, serum urea, uric acid, calcium, albumin, glucose, lipids and iPTH in both groups.

Comparison of CCVD mortality with different levels of serum irisin by Kaplan-Meier survival analysis

The irisin levels revealed a nonnormal distribution and 50.09 ng/mL was the median. Therefore, the median value was selected as a cut-off. The Kaplan-Meier survival curves showed that the mortality in patients with irisin

Table 2 Comparison of baseline characteristics in patients stratified by high and low levels of serum irisin

Variables	Irisin ≤50.09 ng/mL	Irisin >50.09 ng/mL	P value
Cases	74	78	
Age (years)	64.4±15.4	63.5±15.1	0.735
Male/female (n)	45/29	45/33	0.696
HD Vintage (month)	55.4 (18.8, 241.4)	66.5 (18, 308.6)	0.988
Dialysis adquency (KT/V)	1.4±0.6	1.4±0.4	0.855
Systolic pressure (mmHg)	143.4±23.8	144.9±18.0	0.674
Hemoglobin (g/L)	112.1±13.8	112.0±11.4	0.969
Serum creatinine (μmol/L)	916.3±236.8	888.5±225.9	0.501
Serum urea (mmol/L)	26.6±5.3	25.3±5.4	0.178
Serum uric acid (μmol/L)	473.1±93.7	468.3±97.4	0.770
Serum calcium (mmol/L)	2.3±0.2	2.3±0.2	0.712
Serum phosphate (mmol/L)	1.9±0.5	1.8±0.5	0.243
Serum albumin (g/L)	42.0±3.2	41.3±3.9	0.291
Serum glucose (mmol/L)	6.5±1.9	6.9±3.4	0.498
Serum usCRP (mg/L)	3.0 (0.0, 87.5)	2.8 (0.6, 36.8)	0.947
Serum LDL-C (mmol/L)	2.2±0.8	2.1±0.6	0.581
Serum HDL-C (mmol/L)	0.9±0.3	0.9±0.3	0.204
Serum triglycerides (mmol/L)	1.8 (0.4, 6.7)	1.7 (0.1, 10.2)	0.259
Serum total cholesterol (mmol/L)	3.9±1.2	3.9±0.8	0.799
iPTH (pg/mL)	195.6 (17, 3,630)	152.5 (10.0, 1,355)	0.072
CCVD history (with/without)	27/47	20/58	0.148

≤50.9 ng/mL was significantly higher than that in the patients with irisin >50.09 ng/mL (P<0.05) (see *Figure 1*).

Independent determinant factors for CCVD mortality by Cox regression analysis

From our statistical analysis, we found that irisin levels revealed a nonnormal distribution and 50.09 ng/mL was the median. Furthermore, we verified that the median value could predict CCVD mortality by Kaplan-Meier survival curves. Therefore, we used irisin >50.09 *vs.* ≤50.09 ng/mL as a dichotomous variable in the Cox models. Besides, we also selected variables that were statistically significant in *Table 4* and employed Cox regression analysis to find determinant factors for CCVD mortality (P<0.05 included). *Table 5* showed that irisin levels and CCVD history were independent risk factors of CCVD mortality.

Independent determinant factors for all-cause mortality by Cox regression analysis

Variables that were statistically significant in *Table 3* were selected for the Cox regression analysis to find the determinant factors of all-cause mortality (P<0.05 included). The variables included age, systolic pressure, serum creatinine, uric acid, phosphate, albumin, LDL-C, triglycerides, total cholesterol. As shown in *Table 6*, age, systolic pressure and serum creatinine were independent risk factors for all-cause mortality in HD patients.

Discussion

CCVD is a major cause of death in dialysis patients (18,19).

Table 3 Comparison of baseline irisin and other parameters in patients of all-cause death and survival HD patients

Variables	All-cause mortality	Survival	P value
Cases	55	97	
Age (years)	70.9±12.9	60.5±14.8	0.000
Male/female (n)	29/26	60/37	0.272
HD Vintage (month)	66.5 (15, 308.6)	55.8 (20.4, 241.4)	0.253
Dialysis adquency (KT/V)	1.4±0.4	1.4±0.5	0.762
Systolic pressure (mmHg)	152.5±25.7	140.0±16.9	0.002
Hemoglobin (g/L)	110.4±15.1	112.8±10.5	0.273
Serum creatinine (μmol/L)	791.6±233.0	976.5±225.2	0.000
Serum urea (mmol/L)	25.3±7.3	26.8±4.5	0.134
Serum uric acid (μmol/L)	430.3±98.9	483.6±74.3	0.000
Serum calcium (mmol/L)	2.3±0.3	2.4±0.2	0.429
Serum phosphate (mmol/L)	1.8±0.5	2.0±0.5	0.011
Serum albumin (g/L)	40.4±3.7	42.4±3.2	0.001
Serum glucose (mmol/L)	7.1±3.5	6.4±2.1	0.138
Serum usCRP (mg/L)	3.1 (0.7, 36.8)	2.9 (0.0, 87.5)	0.309
Serum LDL-C (mmol/L)	2.0±0.7	2.3±0.7	0.012
Serum HDL-C (mmol/L)	0.9±0.3	0.9±0.3	0.540
Serum triglycerides (mmol/L)	1.5 (0.1, 10.2)	1.8 (0.4, 8.1)	0.043
Serum total cholesterol (mmol/L)	3.6±0.9	4.0±1.0	0.010
iPTH (pg/mL)	174.9 (16, 3,630)	168.2 (10.0, 1,688.0)	0.852
CCVD history (with/without)	22/33	25/72	0.068
Serum irisin (ng/mL)	52.8 (2.2, 352.3)	45.7 (2.1, 367.8)	0.770

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; iPTH, intact parathyroid hormone; usCRP, ultra-sensitive C reactive protein; Kt/V urea, fractional urea clearance.

The traditional risk factors of CCVD in dialysis patients include hypertension, smoking, hyperlipidemia, obesity, and diabetes mellitus, etc. In addition, non-traditional risk factors such as inflammation (20), malnutrition (21), endothelial dysfunction (22), oxidative stress (23), vacular calcification (24), vitamin D deficiency (25), and hyperhomocysteinemia (26) also contribute to the excess risk of CCVD in patients with CKD by triggering vascular injury and endothelial dysfunction. Recently, the levels of ferritin, hemoglobin and doses of iron or erythropoiesis-stimulating agents (ESAs) were also proved to be risk factors of CCVD in HD patients. Furthermore, uraemia-related factors such as abnormal calcium and phosphate metabolism, hyperparathyroidism and newly found Klotho protein all might increase the risk of CCVD among HD patients through affecting vascular calcification and endothelial dysfunction (27). In the present study, we firstly demonstrated that lower levels of irisin were associated with higher CCVD mortality in HD patients. The previous researchers clarified that not only myocardio infarction (4), but also coronary artery disease patients (3) had lower irisin levels than controls in general population. Another study reported that low serum irisin level was an independent predictor of coronary artery severity in patients with stable coronary artery disease (28). El-Lebedy *et al.* discovered that lower levels of irisin were associated with 1.6 times increased CVD risk in patients with type 2 diabetes mellitus (29). Hisamatsu *et al.* emphasized

Table 4 Comparison of baseline irisin and other parameters in HD patients died of CCVD and survival HD patients

Variables	CCVD related deaths	Survival	P value
Cases	18	97	
Age (years)	68.6±15.4	60.5±14.8	0.04
Male/female (n)	6/12	60/37	0.025
HD Vintage (month)	47.2 (18.8, 237.3)	55.8 (20.4, 241.4)	0.583
KT/V urea	1.4±0.2	1.4±0.5	0.84
Systolic pressure (mmHg)	157.7±27.2	140.0±16.9	0.018
Hemoglobin (g/L)	106.2±16.7	112.8±10.5	0.034
Serum creatinine (μmol/L)	725.4±215.2	976.5±225.2	<0.01
Serum urea (mmol/L)	24.2±10.0	26.8±4.5	0.344
Serum uric acid (μmol/L)	459.8±84.7	483.6±74.3	0.293
Serum calcium (mmol/L)	2.3±0.3	2.4±0.2	0.598
Serum phosphate (mmol/L)	1.6±0.4	2.0±0.5	0.013
Serum albumin (g/L)	40.7±4.0	42.4±3.2	0.061
Serum glucose (mmol/L)	6.7±1.9	6.4±2.1	0.664
Serum usCRP (mg/L)	2.2 (0.8, 26.8)	2.9 (0.0, 87.5)	0.765
Serum LDL-C (mmol/L)	1.9±0.7	2.3±0.7	0.134
Serum HDL-C (mmol/L)	0.8±0.2	0.9±0.3	0.294
Serum triglycerides (mmol/L)	1.9 (1.0, 6.7)	1.8 (0.4, 8.1)	0.797
Serum total cholesterol (mmol/L)	3.6±1.0	4.0±1.0	0.103
iPTH (pg/mL)	179.9 (19.0, 3,630.0)	168.2 (10.0, 1,688.0)	0.75
CCVD history (with/without)	11/7	25/72	0.003
Serum irisin (ng/mL)	23.6 (2.2, 319.4)	45.7 (2.1, 367. 8)	0.028

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; iPTH, intact parathyroid hormone; usCRP, ultra-sensitive C reactive protein; Kt/V urea, fractional urea clearance.

higher serum irisin levels were associated with less burden of coronary atherosclerosis, furthermore, in a healthy non-obese population, they consistently found inverse associations of serum irisin levels with the prevalence and progression of coronary artery calcification, regardless of the presence or absence of cardiometabolic risk factors (30). Furthermore, Lee *et al.* (31) demonstrated that serum irisin was significantly associated with carotid atherosclerosis in peritoneal dialysis patients. He *et al.* also found that irisin was associated with increased vascular calcification in HD patients (32). Additionally, Wu *et al.* announced that a low serum irisin level is a predictor of poor early functional outcome in ischemic stroke patients (6). Tu *et al.* also observed that decreased irisin concentration was associated with the poor functional outcome in ischemic stroke and with the increased mortality of stroke (7). However, our study associated irisin levels with CCVD in the specific group, HD patients, in which the CCVD mortality is relatively high. Moreover, according to the results from Cox regression, beside of CCVD history, the well-known risk factor for CCVD mortality in HD patients, low irisin level was proved to be a new independent risk factor which can predict CCVD mortality. Our findings have provided a new point of view to the clinical work.

Furthermore, we also studied the association of irisin with all-cause mortality in HD patients and the results didn't show any association of them. But corresponded to the previous studies (33,34), we found that HD patients

with older age or higher systolic pressure had higher risk of deaths and lower levels of serum creatinine which might represent the poor nutritional status also increased all-cause mortality in HD patients.

What might explain the association of lower irisin levels with CCVD mortality? Firstly, it might because of high blood pressure. Zhang *et al.* (35) found that irisin could regulate blood pressure and be involved in cardiovascular activities. This may be dependent or independent on vascular endothelial cells. Meanwhile, Zhang *et al.* (36) reported that circulating irisin had a negative relationship with blood pressure in patients with preeclampsia. Secondly, lower irisin levels may be associated with more severe endothelial dysfunction. Endothelial dysfunction is considered as the early step in the pathogenesis of atherosclerosis (37). Zhu *et al.* (38) verified that irisin alleviated endothelial dysfunction in type 2 diabetes partially via reducing oxidative/nitrative stresses through inhibiting signaling pathways implicating PKC-β/NADPH oxidase and NF-κB/iNOS, other researchers also demonstrated that irisin could maintain endothelial homeostasis by promoting angiogenesis (39). Thirdly, some researchers found that risin could exert anti-apoptotic effects on ischemic cardiomyocytes by protection of mitochondrial function (40). Moreover, researchers also emphasized that irisin could improve ischemia-induced neuronal injury through the Akt and ERK1/2 signaling pathways activation and contributes to the physical exercise neuroprotective effect against cerebral ischemia (41). Likewise, irisin was proved to have the function of diminishing oxygen-glucose deprivation-induced neuronal injury through inhibiting reactive oxygen species-NOD-like receptor pyrin 3 inflammatory signaling pathway (42).

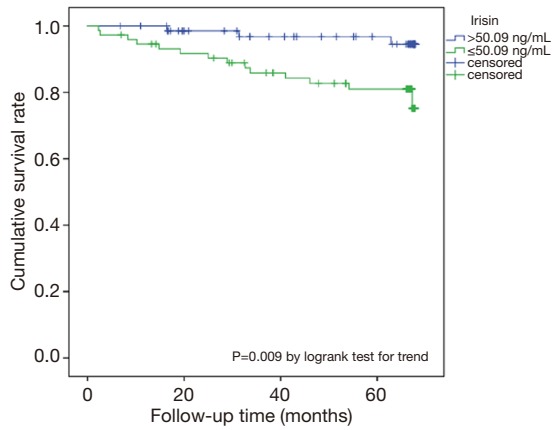

Figure 1 Comparison of CCVD mortalities with different irisin levels by Kaplan-Meier survival analysis. The Kaplan-Meier curve showed that during the follow-up time, the serum irisin levels higher than 50.9 ng/mL had a higher cumulatively survival rate of CCVD. CCVD, cardiovascular and cerebrovascular diseases.

There is still controversy regarding the relatively large variation in irisin concentrations among different ELISA assay kits. Kałużna *et al.* measured the levels of serum irisin in HD patients and the median value was 4.32 μg/mL (43). However, in another study related to irisin in patients with CKD stage 2-4, it was tested that the median values of serum irisin concentrations ranged from 13.00–21.41 ng/mL (44). The reasons of the large variation of serum irisin concentrations in different studies might be attributed to the unclarified changes of irisin level in the body in different physiological or pathological conditions. At present, there hasn't been any evidence indicating any problem with the

Table 5 Cox regression analysis of determinant factors for CCVD mortality

Variables	B	P value	Exp(B)	95% CI for Exp(B)
Age (years)	0.027	0.277	1.027	0.979–1.077
Gender (male/female)	0.662	0.367	1.939	0.460–8.181
Irisin grouping (≤50.09, >50.09 ng/mL)	1.517	0.026	4.560	1.201–17.311
Serum phosphate (mmol/L)	−1.333	0.080	0.264	0.059–1.174
Hemoglobin (g/L)	0.002	0.951	1.002	0.952–1.054
Systolic pressure (≥150, <150 mmHg)	−1.013	0.093	0.363	0.111–1.183
Serum creatinine (μmol/L)	−0.003	0.089	0.997	0.993–1.000
CCVD history (with/without)	1.692	0.010	5.428	1.496–19.697

We selected the median value of irisin and variables that were statistically significant in *Table 4* for the Cox regression analysis.

Table 6 Cox regression analysis of the determinant factors for all-cause mortality in HD patients

Variables	B	P value	Exp(B)	95% CI for Exp(B)
Age (years)	0.035	0.007	1.036	1.010–1.062
Systolic pressure (≥150, <150 mmHg)	0.819	0.006	2.268	1.266–4.062
Serum creatinine (μmol/L)	−0.002	0.019	0.998	0.996–1.000
Serum uric acid (μmol/L)	−0.003	0.135	0.997	0.992–1.001
Serum phosphate (mmol/L)	−0.391	0.270	0.677	0.338–1.355
Serum albumin (g/L)	−0.014	0.770	0.986	0.900–1.081
Serum LDL-C (mmol/L)	−0.051	0.930	0.950	0.303–2.976
Serum triglycerides (mmol/L)	0.157	0.272	1.170	0.884–1.548
Serum total cholesterol (mmol/L)	−0.573	0.222	0.564	0.225–1.413

LDL-C, low density lipoprotein cholesterol.

methodology used to measure irisin. More studies are needed to clarify the inconsistencies in circulating irisin concentrations and to find out the most accurate way to measure irisin concentrations and the standard range for serum irisin.

When interpreting results of this study, some limitations should be taken into account. The small sample size in our study may have prevented our results from reaching a more significant level. Besides, selection bias might occur for this retrospective study. Taken together, multi-center prospective studies are needed to further clarify the association of irisin with CCVD in HD patients.

Conclusions

Our results provided a clinical evidence of the association between lower levels of serum irisin and CCVD mortality in HD patients. Lower levels of serum irisin increased the mortality of CCVD in HD patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of our hospital (No. [2019]130) and individual consent for this retrospective analysis was waived.

References

1. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481:463-8.
2. Polyzos SA, Anastasilakis AD, Efstathiadou ZA, et al. Irisin in metabolic diseases. Endocrine 2018;59:260-74.
3. Anastasilakis AD, Koulaxis D, Kefala N, et al. Circulating irisin levels are lower in patients with either stable coronary artery disease (CAD) or myocardial infarction (MI) versus healthy controls, whereas follistatin and activin A levels are higher and can discriminate MI from CAD with similar to CK-MB accuracy. Metabolism 2017;73:1-8.
4. Aydin S, Aydin S, Kobat MA, et al. Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. Peptides 2014;56:141-5.
5. Deng W. Association of Serum Irisin Concentrations with Presence and Severity of Coronary Artery Disease. Med Sci Monit 2016;22:4193-7.
6. Wu H, Guo P, Jin Z, et al. Serum levels of irisin predict short-term outcomes in ischemic stroke. Cytokine 2019;122:154303.
7. Tu WJ, Qiu HC, Cao JL, et al. Decreased Concentration of Irisin Is Associated with Poor Functional Outcome in Ischemic Stroke. Neurotherapeutics 2018;15:1158-67.
8. Bangalore S, Maron DJ, O'Brien SM, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. N Engl J Med 2020;382:1608-18.
9. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:S112-9.
10. Lee M, Saver JL, Chang KH, et al. Low glomerular filtration rate and risk of stroke: meta-analysis. Bmj 2010;341:c4249.
11. Ovbiagele B, Bath PM, Cotton D, et al. Low glomerular filtration rate, recurrent stroke risk, and effect of renin-angiotensin system modulation. Stroke 2013;44:3223-5.
12. Ebert T, Focke D, Petroff D, et al. Serum levels of the myokine irisin in relation to metabolic and renal function. Eur J Endocrinol 2014;170:501-6.
13. He WY, Wu F, Pang XX, et al. Irisin is Associated with Urotensin II and Protein Energy Wasting in Hemodialysis Patients. Kidney Blood Press Res 2016;41:78-85.
14. Wen MS, Wang CY, Lin SL, et al. Decrease in irisin in patients with chronic kidney disease. PLoS One 2013;8:e64025.
15. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol 2014;10:504-16.
16. Wang XH, Mitch WE. Muscle wasting from kidney failure-a model for catabolic conditions. Int J Biochem Cell Biol 2013;45:2230-8.
17. Moraes C, Marinho SM, da Nobrega AC, et al. Resistance exercise: a strategy to attenuate inflammation and protein-energy wasting in hemodialysis patients? Int Urol Nephrol 2014;46:1655-62.
18. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int 2003;64:603-9.
19. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 1998;32:853-906.
20. Yeun JY, Levine RA, Mantadilok V, et al. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000;35:469-76.
21. Stenvinkel P, Heimbürger O, Paultre F, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999;55:1899-911.
22. Wang AY, Lam CW, Wang M, et al. Circulating soluble vascular cell adhesion molecule 1: relationships with residual renal function, cardiac hypertrophy, and outcome of peritoneal dialysis patients. Am J Kidney Dis 2005;45:715-29.
23. Stenvinkel P, Diczfalusy U, Lindholm B, et al. Phospholipid plasmalogen, a surrogate marker of oxidative stress, is associated with increased cardiovascular mortality in patients on renal replacement therapy. Nephrol Dial Transplant 2004;19:972-6.
24. London GM, Guérin AP, Marchais SJ, et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 2003;18:1731-40.
25. Wang AY, Lam CW, Sanderson JE, et al. Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. Am J Clin Nutr 2008;87:1631-8.
26. Heinz J, Kropf S, Luley C, et al. Homocysteine as a risk factor for cardiovascular disease in patients treated by

dialysis: a meta-analysis. Am J Kidney Dis 2009;54:478-89.
27. Kusano E. Mechanism by which chronic kidney disease causes cardiovascular disease and the measures to manage this phenomenon. Clin Exp Nephrol 2011;15:627-33.
28. Efe TH, Açar B, Ertem AG, et al. Serum Irisin Level Can Predict the Severity of Coronary Artery Disease in Patients with Stable Angina. Korean Circ J 2017;47:44-9.
29. El-Lebedy DH, Ibrahim AA, Ashmawy IO. Novel adipokines vaspin and irisin as risk biomarkers for cardiovascular diseases in type 2 diabetes mellitus. Diabetes Metab Syndr 2018;12:643-8.
30. Hisamatsu T, Miura K, Arima H, et al. Relationship of serum irisin levels to prevalence and progression of coronary artery calcification: A prospective, population-based study. Int J Cardiol 2018;267:177-82.
31. Lee MJ, Lee SA, Nam BY, et al. Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients. Atherosclerosis 2015;242:476-82.
32. He L, He WY, A LT, et al. Lower Serum Irisin Levels Are Associated with Increased Vascular Calcification in Hemodialysis Patients. Kidney Blood Press Res 2018;43:287-95.
33. Chazot C. Dialysis: prognostic value of blood pressure in patients on hemodialysis. Nat Rev Nephrol 2010;6:506-8.
34. Weng CH, Hu CC, Yen TH, et al. Nutritional Predictors of Mortality in Long Term Hemodialysis Patients. Sci Rep 2016;6:35639.
35. Zhang W, Chang L, Zhang C, et al. Central and peripheral irisin differentially regulate blood pressure. Cardiovasc Drugs Ther 2015;29:121-7.
36. Zhang LJ, Xie Q, Tang CS, et al. Expressions of irisin and urotensin II and their relationships with blood pressure in patients with preeclampsia. Clin Exp Hypertens 2017;39:460-7.
37. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899-906.
38. Zhu D, Wang H, Zhang J, et al. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. J Mol Cell Cardiol 2015;87:138-47.
39. Wu F, Song H, Zhang Y, et al. Irisin Induces Angiogenesis in Human Umbilical Vein Endothelial Cells In Vitro and in Zebrafish Embryos In Vivo via Activation of the ERK Signaling Pathway. PLoS One 2015;10:e0134662.
40. Wang H, Zhao YT, Zhang S, et al. Irisin plays a pivotal role to protect the heart against ischemia and reperfusion injury. J Cell Physiol 2017;232:3775-85.
41. Li DJ, Li YH, Yuan HB, et al. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. Metabolism 2017;68:31-42.
42. Peng J, Deng X, Huang W, et al. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. Mol Immunol 2017;91:185-94.
43. Kałużna M, Pawlaczyk K, Schwermer K, et al. Adropin and irisin: New biomarkers of cardiac status in patients with end-stage renal disease? A preliminary study. Adv Clin Exp Med 2019;28:347-53.
44. Sadeghi Shad J, Akbari R, Qujeq D, et al. Measurement of serum irisin in the different stages of chronic kidney disease. Caspian J Intern Med 2019;10:314-9.

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