BMC Nephrology

RESEARCH

Open Access

Association of insulin resistance with chronic kidney disease in individuals without diabetes in a community population in South China

Jiamin Li[1†], Qin Zhou[2†], Zhen Liu[1] and Hequn Zou[3*]

Abstract

Background To explore the relationship of insulin resistance (IR) with chronic kidney disease (CKD) in individuals without diabetes.

Methods We performed a cross-sectional survey among 2142 community-based participants without diabetes from southern China from June to October 2012 and excluded the incomplete data. We divided all the participants into four groups according to the quartiles of homeostasis model assessment of IR (HOMA-IR). Logistic regression models were used to explore the associations of IR with CKD in these subjects.

Results In the unadjusted model, compared with the quartile one group, IR was significantly associated with CKD (odds ratio [OR] = 2.24, $P < 0.001$; OR = 4.46, $P < 0.001$) in the quartile three and four groups, and the association was still significant (OR = 2.08, $P = 0.005$; OR = 3.89, $P < 0.001$) after adjusting for potential confounders (including age, current smoker, current alcohol use, physical inactivity, education level, systolic blood pressure, diastolic blood pressure, serum triglyceride, and body mass index). The area under the receiver operating characteristic curve (95% confidence interval) of HOMA-IR for diagnosing CKD was 0.67 (0.64, 0.71). The cut-off value was 2.5, the sensitivity was 75.2%, and the specificity was 56.4%.

Conclusions IR is associated with Chronic Kidney Disease (CKD) in participants without diabetes. It has been proposed that CKD patients may benefit from reducing their insulin resistance.

Keywords Insulin resistance, Chronic kidney disease, Participants without diabetes

Background

Chronic kidney disease (CKD) has become an important risk factor for global public health and has caused significant economic burden to patients and families. Studies have shown that the global prevalence of CKD is 9.1% [1], and the prevalence of CKD in China is 10.8% [2]. CKD has many aetiologies, such as metabolic syndrome (hypertension, hyperlipidaemia, hyperglycaemia, and obesity), which is closely related to the pathogenesis of CKD. Insulin resistance (IR) is the central link to metabolic syndrome and refers to a pathological state in which insulin promotes glucose uptake and utilisation and reduces the body's responsiveness and sensitivity to

†Jiamin Li and Qin Zhou are co-first author.

*Correspondence:
Hequn Zou
zouhequn@cuhk.edu.cn
[1] Department of Nephrology, Nanfang Hospital Baiyun Branch of Southern Medical University, Guangzhou 510080, People's Republic of China
[2] Department of Nephrology, The Central Hospital of Wuhan, Wuhan 430000, People's Republic of China
[3] School of Medicine, The Chinese University of Hong Kong, Shenzhen 518116, People's Republic of China

the physiological effects of insulin because of genetic and environmental factors [3]. Studies have shown that IR is a common lesion in the early stage of CKD even when the estimated glomerular filtration rate (eGFR) is still within the normal range. IR is closely related to and interacts with CKD; therefore, IR is a risk factor for CKD progression. The severity of IR is directly related to the risk of CKD, and the incidence of CKD increases significantly with the increase in serum insulin level and IR [4–6].

There are still some controversies about the relationship between IR and CKD in individuals without diabetes. At present, few studies with large samples have been conducted on IR and CKD in individuals without diabetes in China. This study is the first to investigate the relationship between IR and CKD in a population in the southern community of China (the original residents of Wanzai community in Zhuhai City).

Methods

Research object

A total of 2142 residents over 18 years old who have lived in Wanzai community of Zhuhai City for more than 10 years and had a local registered residence from June to October 2012 were selected to the stratified random cross-sectional survey. All participants gave their informed consent. This study adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Third Affiliated Hospital of Southern Medical University. The participants underwent oral glucose tolerance test (OGTT) to understand the glucose metabolism of patients, and patients who had no history of diabetes and had fasting plasma glucose (FPG) < 6.1 mmol/L or OGTT 2 h plasma glucose (2-hPG) < 11.1 mmol/L were included in this study. The exclusion criteria were as follows: (1) patients with a history of diabetes and currently taking hypoglycaemic drugs; (2) those with no history of diabetes and had FPG ≥ 6.1 mmol/L or OGTT 2-HPG ≥ 11.1 mmol / L; (3) and those with incomplete data on fasting blood glucose, insulin, blood creatinine, and blood triglycerides. A total of 1691 people were included in the study (Fig. 1).

Research methods

A questionnaire survey was conducted by professional medical staff to record the sex, age, medical history, smoking, and drinking history of all subjects. Residents who completed the information registration were scheduled for the next physical examination, blood collection, and morning urine collection. On the day of the physical examination, the height, body mass, waist circumference, hip circumference, and blood pressure of the residents were measured. The morning urine was collected to assess the urine albumin to creatinine ratio (uACR). In addition, fasting blood sampling was used to measure serum creatinine, uric acid, blood sugar, insulin, blood lipids, etc. The collected samples were uniformly transported to the Experimental Center of the Third Affiliated Hospital of Southern Medical University within 3 h and were stored at 4 °C until detection and application. The CKD-EPI equation was used to calculate the eGFR.

Diagnostic criteria

The CKD diagnostic criteria were as follows [7]: eGFR < 60 mL/min/1.73 m^2 or uACR ≥ 30 mg/g (3 mg/mmol) and lasts for three months or more. eGFR was used to calculate the glomerular filtration rate according to the CKD Epidemiology Collaboration (CKD-EPI) equation of the KDIGO guidelines in the United States.

Formulas used for calculations

IR diagnostic criteria

IR was measured using the homeostasis model assessment of IR (HOMA-IR): HOMA-IR = fasting blood glucose × fasting insulin/22.5. At present, no normal range has been set for HOMA-IR, but its upper limit ranges from two to three in different populations.

CKD-EPI formula:

$$\begin{aligned}
\text{Male}\quad & \text{Scr} \le 0.7\text{mg/dL}\ \text{eGFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{Age}} \\
& \text{Scr} > 0.7\text{mg/dL}\ \text{eGFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{Age}} \\
\text{Female}\quad & \text{Scr} \le 0.9\text{mg/dL}\ \text{eGFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{Age}} \\
& \text{Scr} > 0.9\text{mg/dL}\ \text{eGFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{Age}}
\end{aligned}$$

Statistical treatment

The population was divided into the CKD and non-CKD groups. According to the HOMA-IR quartile, the population was then further divided into four groups (Q1, Q2, Q3, and Q4). Statistical analysis was conducted using SPSS 19.0 software. The measurement data of normal distribution are expressed in mean ± standard deviation. The skewed measurement data are represented by median and interquartile intervals. Enumeration data are expressed as percentages. Analysis of variance was used for the comparison between groups of continuous variables, and the chi-square test was used for the comparison of categorical variables. A multivariate logistic regression model was established to investigate the correlation between IR and CKD. The results are expressed using odds ratio (OR) and 95% confidence interval (CI). Three models were established: model 1 was uncorrected; model 2 was corrected for age, smoking, drinking, and exercise; and model 3 was corrected for age, smoking, drinking, exercise, blood pressure, triglyceride, and body mass index. The performance of the HOMA-IR index in

Fig. 1 Enrollment flow chart

the diagnosis of CKD was analysed using the ROC curve. $P<0.05$ was considered statistically significant.

Results

Ordinary circumstances

A total of 1691 participants were included in the study, and the average age of the participants was 50.84 ± 14.70 years. The prevalence of CKD in the total population was 15.5%. Table 1 shows that the interquartile spacings of HOMA-IR were < 1.13, 1.13–1.64, 1.64–2.42, and > 2.42 for Q1, Q2, Q3, and Q4, respectively. The prevalence rates of CKD were 13.7%, 11.1%, 27.9%, and 47.3% for Q1, Q2, Q3, and Q4, respectively. The prevalence rate of CKD in the HOMA-IR quartile group was statistically different ($P<0.05$).

Basic characteristics of grouping with HOMA-IR interquartile interval

The median HOMA-IR was 1.64. The systolic blood pressure, diastolic blood pressure, body mass index, serum creatinine, fasting blood glucose, blood uric acid, insulin, triglyceride, uACR, and other markers of water level in Q4 of HOMA-IR were higher than those in the other three groups, and the difference was statistically significant ($P<0.05$). However, the level of eGFR in Q4 was lower than that in the other three groups ($P<0.05$; Table 1).

Relationship between HOMA-IR and CKD

In the multifactor logistic regression model, the presence or absence of CKD was used as the secondary dependent variable, and HOMA-IR quartile was used as the rank variable into the regression model. Model 1 is the uncorrected model; model 2 was adjusted for age, smoking, drinking, and exercise; and model 3 was adjusted for age, smoking, drinking, exercise, blood pressure, triglyceride, and body mass index. As shown in Table 2, compared with Q1, the prevalence of CKD in Q3 and Q4 increased significantly (OR = 2.24, $P<0.001$; OR = 4.46, $P<0.001$). After adjusting for age, smoking, drinking, and exercise, the prevalence

Table 1 Baseline characteristics of the subjects according to HOMA-IR quartiles in participants without diabetes

Characteristics	HOMA-IR				*P*
	Quartile one < 1.13 (*n* = 422)	Quartile two 1.13–1.64 (*n* = 423)	Quartile three 1.64–2.42 (*n* = 423)	Quartile four > 2.42 (*n* = 423)	
Age (year)	49.02 ± 14.65	52.80 ± 14.40	53.93 ± 12.50	55.70 ± 11.30	< 0.001
History of hypertension (%)	47 (11.21)	44 (10.40)	69 (16.31)	114 (26.95)	< 0.001
Physical inactivity (%)	154 (36.50)	151 (35.70)	134 (31.68)	159 (37.59)	0.358
Current smoker (%)	67(15.8)	46 (10.87)	44 (10.40)	42 (9.93)	0.149
Current alcohol use (%)	120(28.43)	109 (25.77)	92 (21.75)	101 (23.88)	0.080
SBP (mm Hg)	122.93 ± 20.95	122.35 ± 18.90	130.87 ± 70.42	132.26 ± 18.80	0.001
DBP (mm Hg)	74.36 ± 10.83	77.08 ± 37.37	77.91 ± 11.06	80.95 ± 10.02	0.001
BMI (kg/m^2)	21.24 ± 2.75	21.91 ± 2.93	23.53 ± 3.18	25.07 ± 3.25	< 0.001
Scr (μmol/L)	72.70 ± 16.32	71.50 ± 15.20	71.90 ± 19.50	74.61 ± 16.51	0.044
FBG (mmol/L)	4.47 ± 0.38	4.60 ± 0.34	4.68 ± 0.38	4.86 ± 0.40	< 0.001
uric acid (μmol/L)	331.82 ± 91.03	328.95 ± 82.93	344.92 ± 92.92	381.15 ± 102.75	< 0.001
Insulin (pmol/L)	4.20 ± 0.92	6.75 ± 0.88	9.57 ± 1.30	16.55 ± 5.20	< 0.001
eGFR (mL/min)	101.55 ± 22.58	102.34 ± 21.06	102.70 ± 23.83	98.15 ± 23.92	0.015
uACR (mg/mmoL)	1.35 ± 1.62	1.16 ± 1.32	1.64 ± 2.13	2.30 ± 3.19	< 0.001
TG (mmol/L)	1.08 ± 0.60	1.23 ± 0.70	1.43 ± 0.78	1.95 ± 1.18	< 0.001
CKD (%)	36 (13.7)	29 (11.1)	73 (27.9)	124 (47.3)	< 0.001

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *Scr* serum creatinine, *FBG* fasting blood glucose, *eGFR* estimated glomerular filtration, *uACR* urinary albumin to creatinine ratio; *TG* serum triglyceride

Table 2 Association between HOMA-IR and CKD in participants without diabetes

Quartiles of HOMA-IR	Model one[a]		Model two[b]		Model three[c]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*p*
Quartile one	Reference		Reference		Reference	
Quartile two	0.79 (0.47–1.31)	0.362	0.87 (0.52–1.49)	0.629	0.83(0.46–1.51)	0.547
Quartile three	2.24 (1.46–3.43)	< 0.001	2.54 (1.62–3.99)	0.000	2.08 (1.25–3.49)	0.005
Quartile four	4.46 (2.99–6.66)	< 0.001	4.61 (3.00–7.07)	0.000	3.89 (2.36–6.41)	< 0.001

[a] Unadjusted

[b] Adjusted for age, current smoker, alcohol use, physical inactivity, education

[c] Adjusted for above + systolic blood pressure, diastolic blood pressure, serum triglyceride, and body mass index

rates of CKD in Q3 and Q4 were still higher than Q1 (OR = 2.54, $P < 0.001$; OR = 4.61, $P < 0.001$). After adjusting for systolic blood pressure, diastolic blood pressure, triglyceride, and body mass index, the prevalence of CKD in the third and fourth groups still increased significantly compared with the lowest quartile array (OR = 2.08, $P = 0.005$; OR = 3.89, $P < 0.001$). The results suggest that IR is independently related to CKD in participants without diabetes.

ROC curve evaluation of the efficacy of HOMA-IR in predicting CKD in participants without diabetes

By using HOMA-IR as the detection variable, the area under the curve (95% CI) for CKD diagnosis was 0.67 (0.64, 0.71), the sensitivity was 75.2%, and the specificity was 54.6%. The cut-off value of HOMA-IR diagnosis for CKD is 2.5 (Fig. 2).

Discussion

IR is a pathological state caused by genetic and environmental factors in which insulin promotes glucose uptake and utilisation and causes the body to be less responsive and sensitive to the physiological action of insulin. It mainly acts on the liver, fat, and muscle tissue. The resulting glucose and lipid metabolism disorder can lead to diabetes, coronary heart disease, obesity, metabolic syndrome, and other metabolic disorders [3]. IR not only

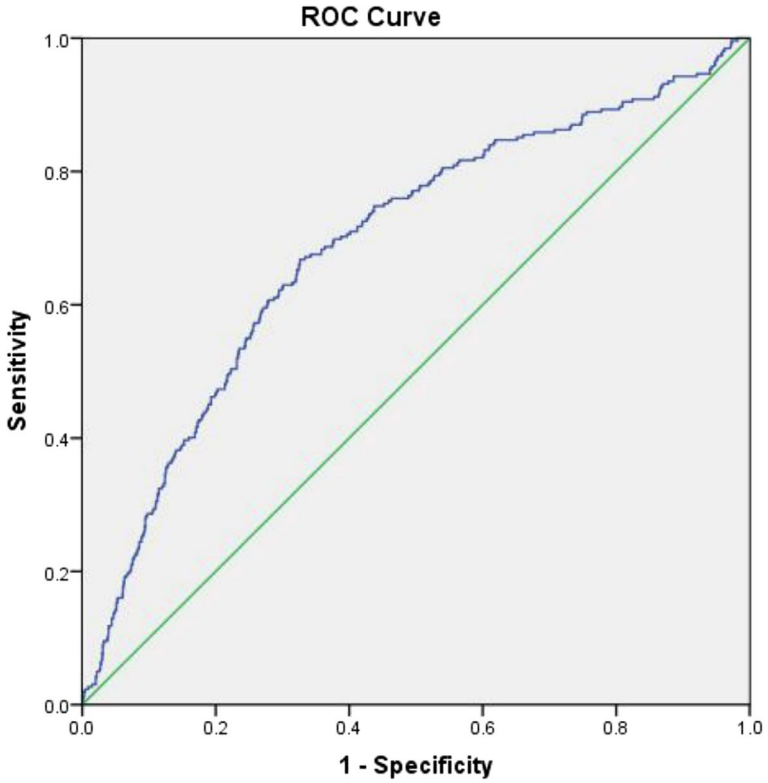

Fig. 2 ROC curve analysis of HOMA-IR in predicting CKD

exists in diabetes but also in patients with non-diabetes kidney disease, thus increasing the risk of early death in CKD patients [8, 9]. IR can exist at any stage of CKD and is a common complication of patients undergoing haemodialysis and peritoneal dialysis [10]. IR in CKD patients is caused by multiple factors, such as exercise, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anaemia, lipid metabolism disorder, and intestinal flora disorder [4, 11–13]. The occurrence and progress of CKD caused by IR are also affected by multiple pathogenic mechanisms. Hyperinsulinemia can lead to glomerular ultrafiltration, endothelial dysfunction, and increased vascular permeability via the insulin-like growth factor-1 pathway, thus leading to proteinuria. At the same time, it can also promote renal fibrosis via transforming growth factor beta. In patients without diabetes, even short-term insulin injections will increase urinary protein excretion. On the contrary, the protein in the renal tubule may cause tubulointerstitial damage and fibrosis [14–17].

In the current study, we found that a higher HOMA-IR index is correlated with a higher risk of CKD. IR is an independent risk factor for CKD in people without diabetes in southern China. However, the relationship between IR and CKD is still controversial in people without diabetes. A study in the United States found that the risk of CKD increased with the increase in the HOMA-IR index in middle-aged individuals without diabetes [9]. Landau et al. [18] found that HOMA-IR was negatively correlated with eGFR in individuals without diabetes with eGFR < 60 ml/min/1.73 m. Wang et al. [19] observed 286 patients without diabetes but with stage 1–3 CKD and found that HOMA-IR was positively correlated with urea nitrogen and serum creatinine levels in patients with early renal insufficiency and was negatively correlated with eGFR. A nine-year follow-up study found that the incidence of CKD increased significantly with the increase in serum insulin and IR levels in slightly overweight patients without diabetes [4]. The results of a single-centre study in Japan show that IR can predict the risk of death in 170 patients without diabetes who are undergoing dialysis [10]. All the above studies indicate that IR is a risk factor for CKD, which is consistent with the conclusion of the current study. However, a cross-sectional study of 574 participants without diabetes in the United States showed that the prevalence of CKD in a population with metabolic syndrome was high; however, only hypertension was associated with the prevalence of CKD in each component of metabolic syndrome

($P < 0.05$), and IR was not an independent risk factor for CKD [20]. They believed that the main reason for the difference between this study and the previous study was that this study diagnosed IR by using the direct detection method of the insulin inhibition test. The vast majority of IR detection uses indirect methods, such as HOMA-IR, to diagnose IR. Compared with direct detection methods, the variability of HOMA-IR detection methods is less than 40%. This may be the main reason for the inconsistent results.

Conclusions

The results of this study indicate that IR is associated with CKD in participants without diabetes. It has been proposed that CKD patients may benefit from reducing their insulin resistance. At present, few studies with large sample sizes have been conducted on IR and CKD in individuals without diabetes in China. This study is the first to conduct an epidemiological survey in the community population of southern China (the original residents of Wanchai community in Zhuhai City) to explore the relationship between IR and CKD. This study provides evidence regarding the relationship between IR and CKD in individuals without diabetes from the perspective of epidemiology and provides guidance for the prevention and treatment of chronic diseases. However, given that this study was not able to explore the relationship between insulin resistance and CKD in chronic inflammatory state due to the lack of data on chronic inflammation-related indicators such as CRP and IL-6, and this study is a cross-sectional survey, the sampling population was limited, and the random sample is only representative. It is necessary to conduct long-term prospective research, and Inflammatory markers will be also included, to further clarify the value of IR in predicting CKD in individuals without diabetes.

Abbreviations

IR	Insulin resistance
CKD	Chronic kidney disease
HOMA-IR	Homeostasis model assessment of IR
eGFR	Estimated glomerular filtration rate
OGTT	Oral glucose tolerance test
FPG	Fasting plasma glucose
2-hPG	2 h plasma glucose
uACR	Urine albumin to creatinine ratio
Scr	Serum creatine

Acknowledgements

Thanks to Experimental Center of the Third Affiliated Hospital of Southern Medical University for providing inspecting.

Authors' contributions

JL and QZ were responsible for the study design, reviewed the literature. JL drafted and revised the manuscript, created the figures, and translated the manuscript. JL and ZL collected the samples and data . HZ provided critical comments. All authors edited and finalized the manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (81270840) and the Clinical Research Cultivation Project of Southern Medical University (LC2016PY047).

Data availability

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The experimental scheme was approved by the ethics committee of the Third Affiliated Hospital of Southern Medical University (201,708,011). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 7 April 2024 Accepted: 18 November 2024
Published online: 30 November 2024

References

1. Wang V, Vilme H, Maciejewski ML, Boulware LE. The economic burden of chronic kidney disease and end-stage renal Disease. Semin Nephrol. 2016;36(4):319–30.
2. Zhang L, Zhao MH, Zuo L, Wang Y, Yu F, Zhang H et al. China Kidney Disease Network (CK-NET) 2016 Annual Data Report. Kidney Int Suppl (2011). 2020;10(2):e97-185.
3. Jung SH, Jung CH, Reaven GM, Kim SH. Adapting to insulin resistance in obesity: role of insulin secretion and clearance. Diabetologia. 2018;61(3):681–7.
4. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol. 2003;14(2):469–77.
5. Conkar S, Mir S. Relationship of insulin resistance to vitamin d status in children with nondiabetic chronic kidney disease. Saudi J Kidney Dis Transpl. 2017;28(5):1078–84.
6. Wakino S, Minakuchi H, Miya K, Takamatsu N, Tada H, Tani E, et al. Aldosterone and insulin resistance: vicious combination in patients on maintenance Hemodialysis. Ther Apher Dial. 2018;22(2):142–51.
7. Kumar BV, Mohan T. Retrospective comparison of estimated GFR using 2006 MDRD, 2009 CKD-EPI and Cockcroft-Gault with 24 Hour urine creatinine Clearance. J Clin Diagn Res. 2017;11(5):C9–12.
8. de Boer IH, Zelnick L, Afkarian M, Ayers E, Curtin L, Himmelfarb J, et al. Impaired glucose and insulin homeostasis in moderate-severe CKD. J Am Soc Nephrol. 2016;27(9):2861–71.
9. Cao W, Shi M, Wu L, Yang Z, Yang X, Liu H, et al. A renal-cerebral-peripheral sympathetic reflex mediates insulin resistance in chronic kidney disease. EBioMedicine. 2018;37:281–93.
10. Xu H, Carrero JJ. Insulin resistance in chronic kidney disease. Nephrol (Carlton). 2017;22 Suppl 4:31 – 4.
11. Juszczak F, Caron N, Mathew AV, Declèves AE. Critical role for AMPK in Metabolic Disease-Induced chronic kidney Disease. Int J Mol Sci. 2020;21(21):7994.
12. Guthoff M, Wagner R, Vosseler D, Peter A, Nadalin S, Häring HU, et al. Impact of end-stage renal disease on glucose metabolism-a matched cohort analysis. Nephrol Dial Transpl. 2017;32(4):670–6.
13. Tan Z, Ye Z, Zhang J, Chen Y, Cheng C, Wang C, et al. Serum irisin levels correlated to peritoneal dialysis adequacy in nondiabetic peritoneal dialysis patients. PLoS ONE. 2017;12(4):e176137.
14. Tahar A, Zerdoumi F, Saidani M, Griene L, Koceir EA. [Effects of oral vitamin D(3) supplementation in stage 3 chronic kidney disease subjects: insulin

resistance syndrome and hormonal disturb interactions]. Ann Biol Clin (Paris). 2018;76(3):313–25.
15. Roshanravan B, Zelnick LR, Djucovic D, Gu H, Alvarez JA, Ziegler TR, et al. Chronic kidney disease attenuates the plasma metabolome response to insulin. JCI Insight. 2018;3(16):e122219.
16. Pammer LM, Lamina C, Schultheiss UT, Kotsis F, Kollerits B, Stockmann H, et al. Association of the metabolic syndrome with mortality and major adverse cardiac events: a large chronic kidney disease cohort. J Intern Med. 2021;290(6):1219–32.
17. Chalupsky M, Goodson DA, Gamboa JL, Roshanravan B. New insights into muscle function in chronic kidney disease and metabolic acidosis. Curr Opin Nephrol Hypertens. 2021;30(3):369–76.
18. Landau M, Kurella-Tamura M, Shlipak MG, Kanaya A, Strotmeyer E, Koster A, et al. Correlates of insulin resistance in older individuals with and without kidney disease. Nephrol Dial Transpl. 2011;26(9):2814–19.
19. Wang CJ, Bao XR, Du GW, Wang Y, Chen K, Shen ML, et al. Effects of insulin resistance on left ventricular hypertrophy in patients with CKD stage 1–3. Int Urol Nephrol. 2014;46(8):1609–17.
20. Johns BR, Pao AC, Kim SH. Metabolic syndrome, insulin resistance and kidney function in non-diabetic individuals. Nephrol Dial Transpl. 2012;27(4):1410–5.

Publisher's Note