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Effect of limb ischemic preconditioning on the indirect index of insulin resistance in maintenance hemodialysis patients

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Abstract

Background Poor prognosis of maintenance hemodialysis (MHD) patients, including cardiovascular disease (CVD) and protein-energy wasting (PEW), is strongly associated with insulin resistance (IR). Previous studies have revealed that limb ischemic preconditioning (LIPC), as an intervention, is effective in reducing inflammation and oxidative stress levels in patients. The aim of this study was to elucidate the effects of LIPC on IR indirect indices, inflammation and oxidative stress indices, and to further explore the potential mechanisms of LIPC in reducing IR indices.

Methods A retrospective analysis was performed on 62 patients with MHD who had previously undergone limb ischemia preconditioning (LIPC) or sham surgery (Sham). General clinical and laboratory data were collected. Furthermore, to assess the IR status of MHD patients, the following indices were employed: triglyceride-glucose index (TyG), triglyceride-glucose body mass index (TyG-BMI), triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), and metabolic score of insulin resistance (METS-IR). Inflammation and oxidative stress indicators included high-sensitivity C-reactive protein (hs-CRP), hs-CRP /albumin ratio (CAR), serum malondialdehyde (MDA) and superoxide dismutase (SOD). Mediation analysis was conducted using Model 4 in the SPSS PROCESS macro version 4.1.

Results Following a four-week experiment, hs-CRP (15.46 ± 3.60 vs. 10.53 ± 5.42, $p < 0.001$), CAR (0.39 ± 0.10 vs. 0.26 ± 0.13, $p < 0.001$) and MDA (8.46(6.71,9.85) vs. 5.99(5.11,7.89), $p = 0.001$) indices were significantly decreased in the MHD patients of the LIPC group, whereas SOD indices (215.07(180.27,286.45) vs. 267.76(228.32,319.54), $p = 0.012$) were significantly higher. Only hs-CRP (-4.93 ± 5.68 vs. 0.16 ± 5.39, $p = 0.001$) and CAR (-0.14 ± 0.14 vs. -0.001 ± 0.15, $p = 0.001$) were significantly different in the LIPC group compared to the Sham group. In contrast, the changes in MDA ($p = 0.058$) and SOD ($p = 0.107$) were not statistically significant between groups. The intra- and inter-group differences in the four indirect indices of IR were significant ($p < 0.05$). The heatmap revealed a notable correlation between the changes in hs-CRP and CAR levels and the changes in the IR indirect indices. In addition, The mediation model showed that the inflammatory indicators hs-CRP played a partial mediating role in the improvement of IR indices (TyG-BMI) by LIPC.

Conclusion LIPC has an excellent ability to inhibit inflammation and peroxidation. In addition, in MHD patients, inflammation plays a significant role in the process of LIPC improving IR index.

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Introduction

The incidence and prevalence of chronic kidney disease (CKD) is increasing at an alarming rate globally, as is the number of complications associated with it. Patients with CKD frequently suffer from cardiovascular disease (CVD) and protein-energy wasting (PEW), particularly in ESRD, where all-cause mortality is significantly higher [1]. Insulin resistance (IR), which is defined as reduced or impaired insulin sensitivity in target organs or tissues, manifested by impaired glucose uptake and oxidation, is an essential risk factor in the pathogenesis of diabetes mellitus and cardiovascular disease [2]. Notably, several clinical outcomes (cardiovascular disease, death [3], and protein energy expenditure [4]) in ESRD patients receiving hemodialysis have been associated with IR. IR its self is a risk for CVD and strongly associates with other CVD risks (dyslipidemia, hypertension, and inflammation). In ESRD patients undergoing hemodialysis, the cardiovascular risks worsen the arterial stiffness which contributes to the development of cardiovascular events and diseases [3]. In addition, protein metabolism is profoundly affected by insulin signaling as well. The activation of insulin receptor, in concert with insulin growth factor-1 receptor, activates PI3K and PKB/Akt which in turn promotes protein synthesis [5]. Thus, resistance to the protein anabolic effects of insulin may be an important factor contributing to PEW in MHD patients. Nonetheless, the etiology and mechanisms that lead to IR are complex and involve numerous factors, and yet some of the more well-defined mechanisms include inflammation and oxidative stress [6].

Ischemic preconditioning (IPC) is a straightforward, safe, and well-tolerated intervention, originally introduced to the heart as a protective measure against the harmful effects of myocardial ischemia/reperfusion, as described by Murry and colleagues in 1986. IPC is an endogenous protective mechanism in which brief periods of ischemia or hypoxia safeguard the heart from subsequent, more prolonged ischemic damage [7]. Subsequently, IPC has been demonstrated to be effective in other tissues as well. In a meta-analysis, Jiachang included 30 randomized controlled trials covering a total of 7,244 patients. The results showed that IPC significantly reduced the risk of acute kidney injury in patients undergoing cardiac and vascular interventions compared to controls [8]. In a series of studies to improve complications of MHD, we found that IPC was effective in reducing the incidence of hypotension in MHD patients [9]. In addition, by suppressing oxidative stress and inflammation, IPC was able to improve sleep disorders in MHD patients [10]. In the continuous development of IPC, limb ischemic preconditioning (LIPC) has been developed based on IPC. Compared with direct IPC, LIPC has the advantage of protecting without direct stress on the target organ [11]. A recent study evaluating the optimal IPC regimen demonstrated that LIPC provided superior protection when the number and duration of ischemic episodes were maintained constant [7]. The inhibitory effects of LIPC on inflammation and oxidative stress have attracted our attention, and therefore it is envisioned to improve IR in MHD patients by LIPC.

Practical indirect indicators of insulin sensitivity have been validated in MHD patient populations [12–14]. For instance, the triglyceride-glucose index (TyG) [15], the triglyceride-glucose body mass index (TyG-BMI) [16], the triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C) [17], and the metabolic score for insulin resistance (METS-IR) [18] are examples. In the present study, we will use these four indices to reflect IR. Given that the pathogenesis of IR is closely related to inflammation and oxidative stress, LIPC has also indicated positive effects in ameliorating inflammation as well as oxidative stress [19, 20]. We hypothesized that LIPC may improve the IR index in MHD patients by reducing inflammation and oxidative stress. Therefore, the aim of this study was to assess the efficacy of LIPC in reducing IR in MHD patients, to explore in depth its specific effects on inflammation and oxidative stress status, and to validate the role of inflammation and oxidative stress in the pathway of LIPC in improving IR indices.

Method

Experimental design

This study is a retrospective analysis, with data collected from patients who implemented LIPC intervention and sham surgery (Sham) intervention from November 2022 to June 2023 in this subject group (Fig. 1). The inclusion criteria were as follows: (1) age greater than or equal to 18 years and less than 80 years; (2) duration of continuous dialysis greater than 3 months; (3) All patients maintained a stable medication regimen throughout the study period, with no dosage adjustments. The exclusion criteria were as follows: (1) patients with type 1 diabetes mellitus; (2) patients taking medication to lower triglycerides (fenofibrate); (3) patients in an acute state of infection or undergoing anti-inflammatory therapy were excluded; (4) patients receiving hormonal and/or immunosuppressive therapy were excluded; (5) patients with insufficient dialysis dose (single cell $Kt/V < 1.2$); (6) patients receiving hemoperfusion during the study period; (7) patients

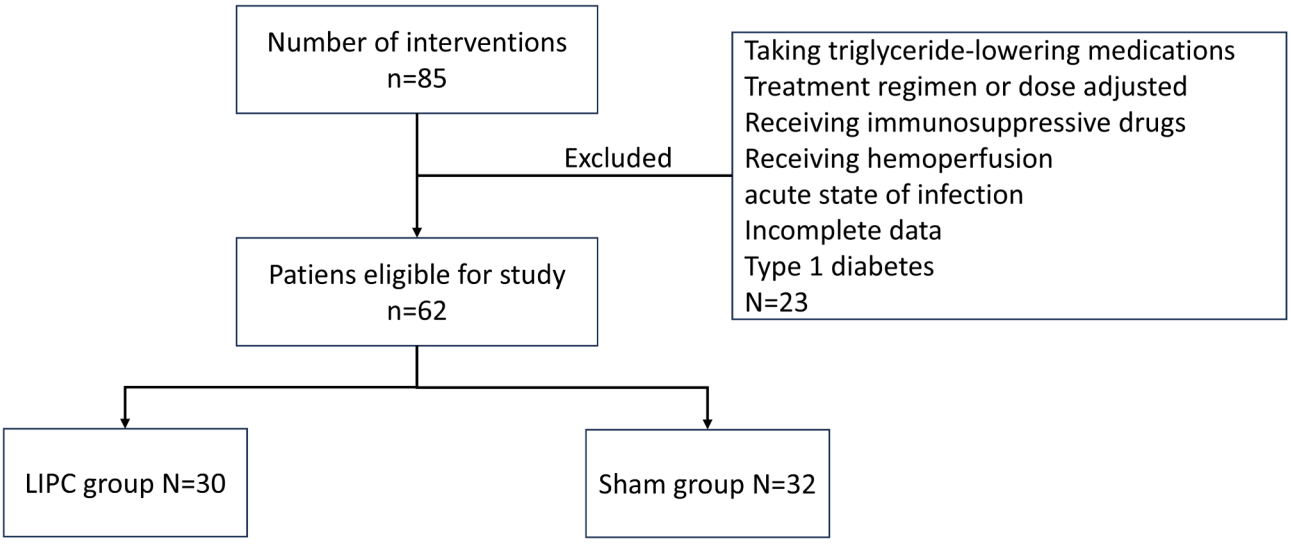

Fig. 1 Flow chart of patient selection

with incomplete clinical and laboratory data. The study received approval from the Medical Ethics Committee of Changzhou Second People's Hospital ([2023]KY213-01).

Limb ischemia pretreatment program

The patient was positioned supine, with the lower limb on the operative side elevated such that the angle between the femur and the bed was approximately 30–45 degrees, and LIPC (LIPC group) or sham LIPC (control group) was performed once a day utilizing a LIPC device (RIP-906D, Nanfo Science and Technology Co., Ltd., Shenzhen, China). Blood pressure at the point of pressurization was measured prior to and following the procedure to observe the effectiveness of the intervention. LIPC: The LIPC cuff was applied to the patient's femur (left or right) near the knee joint and inflated and pressurized for 5 min (200 mmHg), subsequently relaxed for 5 min (0 mmHg) for five consecutive cycles, for a total of 50 min. Pseudo-LIPC operation: the operation was the same as the LIPC operation except that the pressurization pressure of 20mmHg caused pseudo-ischemia of the limb. In both groups, the lower limb undergoing intervention was rotated daily to ensure both limbs received sufficient peripheral treatment over a 4-week period. Each participant received comprehensive instructions on how to operate the LIPC device. Patient usage and any changes in clinical symptoms were closely monitored on a daily basis through WeChat.

Data collection and definition

General patient information and laboratory test data were obtained from the healthcare system. General information included age, sex, height and weight (prior to and following each hemodialysis session), past medical history, baseline medication, as well as duration of hemodialysis. Laboratory tests included glycosylated hemoglobin, PTH, albumin, glucose, urea nitrogen, creatinine, uric acid, total cholesterol, triglycerides, HDL, LDL, and KT/V at baseline and the end of the intervention. Besides, inflammation and oxidative stress indices included high-sensitivity C-reactive protein (hs-CRP), serum malondialdehyde (MDA), and superoxide dismutase (SOD), were detected by enzyme-linked immunosorbent assay (ELISA). All laboratory data were collected from blood samples taken from patients prior to the initiation of fasting and short-gap dialysis. CAR was calculated from hs-CRP/albumin. The urea clearance index (Kt/V) values were calculated using the Daugirdas single-compartment model equation. Body mass index (BMI) was calculated as weight (kg) divided by height (m2) squared. The IR index was calculated according to the following formula: TyG index = Ln [TG (mg/dL) × FBG (mg/dL) ÷ 2]; TyG-BMI index = TyG × BMI (kg/m2); TG/HDL-C = TG (mg/dl) ÷ HDL-C (mg/dl); METS-IR = Ln [(2 × FBG (mg/dl)) + TG (mg/dl)] × BMI (kg/m2) ÷ Ln [HDL-C (mg/dl)].

Statistical analysis

In this paper, PASS2021 software was used to calculate the sample size. Based on evidence from the relevant literature and preliminary experimental results [10], based on a set setting of bilateral $\alpha = 0.05$, power of test = 90%, and a remission rate of approximately 10% in the control group and up to 55% in the LIPC-treated group. Subjects in the experimental and control groups were distributed in a 1:1 ratio with a withdrawal rate of 20%. Hence, the estimated total sample size should be no less than 46 subjects.

Data were analyzed employing SPSS version 26.0. Normally distributed continuous variables are expressed as

mean and standard deviation. Non-normally distributed continuous variables are presented as median values with interquartile ranges. Categorical variables are reported as frequencies and percentages. To compare the two groups of normal variables, an independent samples t-test was employed, while for skewed and categorical variables, the Mann-Whitney U-test, chi-square test and Fisher's exact test were employed. Furthermore, Outcome variables before and after the intervention were tested using the paired samples t-test and Wilcoxon paired rank test, respectively. Analysis of covariance (ANCOVA) tests were adopted to determine the level of significant difference between the two groups after the intervention while adjusting for baseline measurements, age and BMI. Post hoc analyses were conducted using the Bonferroni-Dunn method to correct for multiple comparisons. Spearman rank correlation analyses were employed to evaluate the relationships between changes in indicators of insulin resistance, inflammation, and oxidative stress, with the results visualized using Origin software. Model 4 in the SPSS plug-in PROCESS 4.1 was used to test for mediated effects. Sensitivity analyses were conducted to adjust for confounders. The following three models were included. Model1: unadjusted for covariates. Model2: adjusted for age, sex, BMI, glucose-lowering medication, insulin. Model3: adjusted for age, sex, BMI, glucose-lowering medication, insulin, blood glucose, urea nitrogen, creatinine, uric acid, albumin, HDL-C, and triglycerides. A two-sided $p < 0.05$ was considered significant.

Result

Comparison of baseline data between the LIPC group and sham group

In this study, the final 62 MHD patients [LIPC ($n = 30$) and sham ($n = 32$)] were included in the analysis. The baseline characteristics of the patients are indicated in Table 1, the distribution of gender, mean age, BMI, laboratory characteristics, and the number of years on dialysis were not significantly different between the two groups ($p > 0.05$).

Comparison of inflammation and oxidative stress indices between the LIPC and Sham groups during the study period

Changes in inflammation and oxidative stress indices in patients before and after the LIPC or Sham intervention

Table 1 Baseline characteristics of subjects in the LIPC and Sham groups

	LIPC($n = 30$)	Sham($n = 32$)	*P*
Age, (years)	56.93 ± 14.39	53.44 ± 11.10	0.287
Males, *n* (%)	20(66.7)	18(56.3)	0.4
SBP, (mmHg)	147.03 ± 21.61	140.88 ± 22.36	0.275
DBP, (mmHg)	86.57 ± 12.67	85.84 ± 12.22	0.82
HR, (beats/min)	79.00(72.75,84.00)	78.50(76.00,83.75)	0.507
BMI, (kg/m2)	22.15(20.30,24.55)	21.96(20.24,25.51)	0.978
Smoking History, (%)	12(40.0)	10(31.3)	0.472
Duration of dialysis, (months)	48(24,93)	37(21,81)	0.621
Hypertension, n(%)	29(96.7)	31(96.9)	1.0
DM, *n* (%)	9(30.0)	10(31.3)	0.915
statin drug, n(%)	14(46.7)	15(46.9)	0.987
insulin, n(%)	5(15.6)	6(18.8)	0.83
antihyperglycemic drug, n(%)	2(6.7)	1(3.1)	0.516
Glycated hemoglobin, (%)	5.50(5.28,5.88)	5.75(5.33,6.10)	0.142
Hemoglobin, (g/L)	105.17 ± 15.05	111.56 ± 15.92	0.11
PTH, (ng/L)	172.55(112.00,337.53)	229.20(84.78,389.38)	0.583
Albumin, (g/L)	39.91 ± 3.59	40.10 ± 4.37	0.858
glucose, (mmol/L)	5.66(4.74,6.73)	5.40(4.70,6.99)	0.8
BUN, (mmol/L)	22.01 ± 10.05	21.65 ± 6.95	0.871
Creatinine, (μmol/L)	818.97 ± 297.15	869.07 ± 230.80	0.46
UA, (μmol/L)	349.33 ± 142.65	360.48 ± 107.00	0.728
TC, (mmol/L)	4.00(3.64,5.16)	3.81(3.07,4.32)	0.17
Triglyceride, (mmol/L)	1.53(1.35,2.37)	1.47(1.03,2.04)	0.118
HDL-C, (mmol/L)	1.00(0.75,1.15)	1.04(0.84,1.19)	0.36
LDL-C, (mmol/L)	2.17(1.88,2.86)	1.94(1.47,2.61)	0.13
spKt/V	1.34 ± 0.09	1.32 ± 0.08	0.461

Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]

SBP, Systolic Blood pressure; DBP Diastolic Blood pressure; HR heart rate; BMI Body mass index; BUN blood urea nitrogen; UA uric acid; TC Total Cholesterol; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol

during the 4-week trial are illustrated in Table 2. At the start of the study, no significant differences were observed between the groups ($p > 0.05$). At the end of the 4-week intervention, within-group comparisons showed significant reductions in hs-CRP and CAR ($p < 0.001$) in the LIPC group. In addition, LIPC significantly reduced hs-CRP and CAR levels compared to the Sham group, and this result remained significant between study groups even after adjusting for baseline values, age, and BMI. Despite the fact that the oxidative indices MDA and SOD were substantially altered in the within-group comparison, the changes in MDA and SOD did not reach significant levels in comparison to the Sham group ($p > 0.05$).

Comparison of insulin resistance index between LIPC and sham groups during the study period

Changes in IR indices at the beginning and end of the trial are illustrated in Table 3. No significant changes were observed in the baseline distribution of IR indices between patients in the LIPC and sham groups ($p > 0.05$). After the 4-week intervention, within-group comparisons indicated significant reductions in TyG ($p < 0.001$), TyG-BMI ($p < 0.001$), and TG/HDL-C ($p = 0.007$) in the LIPC group, while METS-IR ($p = 0.03$) was also significantly lower. There were differences in TyG ($p < 0.001$), TyG-BMI ($p < 0.001$), TG/HDL-C ($p < 0.001$), as well as METS-IR ($p = 0.03$) between the two groups. Between-group differences in the four indices remained statistically significant, even after adjusting for baseline values, age, and BMI. In summary, after a 4-week intervention, LIPC significantly reduced hs-CRP, CAR, and MDA levels as well as indirect indicators of insulin resistance in MHD patients, while significantly elevating SOD levels.

Correlation analysis of inflammation and oxidative stress indexes and IR index change values during the study period

The correlation between LIPC or Sham intervention mode, inflammation and oxidative stress change values, and IR change values are revealed in Fig. 2. The results demonstrated that with the implementation of LIPC intervention, the less hs-CRP, the lower the IR index. Changes between IR indices (TyG, TyG-BMI, TG/HDL-C, METS-IR) were all significantly correlated. Surprisingly, no significant correlation was observed between the change in SOD values and the mode of intervention or the IR index. However, one of the change values in

Table 2 Intra- and inter-group comparisons of inflammation and oxidative stress indices in subjects before and after intervention in LIPC and Sham groups

	LIPC[a] ($n = 30$)	Sham[a] ($n = 32$)	*P*-value[b] (between)
hs-CRP (mg/ml)			
Baseline	15.46 ± 3.60	14.12 ± 5.36	0.256
Endpoint	10.53 ± 5.42	14.28 ± 7.88	0.034
Change[c]	-4.93 ± 5.68	0.16 ± 5.39	0.001
P value[d] (within)	<0.001	0.867	0.002[e]
CAR			
Baseline	0.39 ± 0.10	0.35 ± 0.12	0.158
Endpoint	0.26 ± 0.13	0.35 ± 0.20	0.034
Change	-0.14 ± 0.14	-0.001 ± 0.15	0.001
P value (within)	<0.001	0.958	0.002
MDA (nmol/ml)			
Baseline	8.46(6.71,9.85)	7.73(6.79,9.74)	0.545
Endpoint	5.99(5.11,7.89)	7.39(5.30,9.99)	0.21
Change	-1.84(-3.14,-0.69)	-1.11(-2.18,1.61)	0.058
P value (within)	0.001	0.314	0.116
SOD (pg/ml)			
Baseline	215.07(180.27,286.45)	226.71(195.33,260.19)	0.622
Endpoint	267.76(228.32,319.54)	242.41(181.08,283.86)	0.128
Change	60.26(-8.90,98.58)	-6.86(-36.71,74.92)	0.107
P value (within)	0.012	0.239	0.165

[a] Values are expressed as mean ± standard deviation or median (25th, 75th percentiles)

[b] *P*-value for comparing the values between the study groups at baseline, at the endpoint and the change from baseline. Two sample t-test and Mann–Whitney U test were used for parametric and non-parametric comparisons, respectively

[c] Endpoint values minus the baseline ones

[d] *P*-value for comparing baseline with the end point values within each group. Paired sample t-test and Wilcoxon Paired Rank test were used for parametric and non-parametric comparison, respectively

[e] *P* value for ANCOVA test to determine the significant levels of differences between the two groups post-intervention while adjusting for baseline measurements, age, and BMI

Table 3 Intra- and inter-group comparison of insulin resistance indices in subjects before and after intervention in LIPC and Sham groups

	LIPC[a] (*n* = 30)	Sham[a] (*n* = 32)	*P*-value[b] (between)
TyG			
Baseline	9.04 ± 0.57	8.82 ± 0.59	0.148
Endpoint	8.54 ± 0.58	8.76 ± 0.51	0.123
Change[c]	-0.50 ± 0.40	-0.07 ± 0.39	<0.001
Pvalue[d](within)	<0.001	0.356	<0.001[e]
TyG-BMI			
Baseline	198.66(182.08,230.62)	198.49(171.16,226.24)	0.632
Endpoint	188.92(161.15,214.02)	195.25(174.62,225.51)	0.284
Change	-16.52(-21.78,-5.71)	5.30(-6.52,9.47)	<0.001
P value(within)	<0.001	0.443	<0.001
TG/HDL			
Baseline	4.04(2.87,5.65)	2.98(1.90,4.58)	0.081
Endpoint	3.30(2.00,4.81)	3.29(1.97,5.20)	0.554
Change	-0.58(-1.69,-0.06)	0.38(-0.24,1.18)	<0.001
P value(within)	0.007	0.112	0.018
METS-IR			
Baseline	36.25(33.09,41.33)	35.98(30.34,42.57)	0.545
Endpoint	33.61(30.14,40.43)	35.34(32.97,41.22)	0.345
Change	-1.32(-3.90,0.84)	0.65(-1.51,2.78)	0.03
P value(within)	0.03	0.369	0.032

Data analysis as in Table 2

SOD showed a trend toward significance with the LIPC intervention ($P = 0.107$).

Mediating role of inflammation in the reduction of IR index by LIPC

The relationship between intervention modality, inflammation, and IR change values was analyzed, revealing a correlation between the LIPC intervention and the IR index, as well as an association between the LIPC intervention and changes in inflammation values. In addition, the inflammation change value affected the IR index. Therefore, the value of change in IR index was used as the outcome variable, LIPC or Sham intervention modality as the independent variable, and hs-CRP and CAR as the mediating variables. A mediating effect was considered significant if the 95% confidence interval (CI) did not include zero. Bootstrap test results indicated that hs-CRP and CAR played a partial mediating role in the improvement of IR indices (TyG and TyG-BMI) by LIPC. However, this mediating effect was not present in TG/HDL-C, METS-IR (results not shown).

Sensitivity analysis

To assess the robustness of the mediation model, we implemented a sensitivity analysis and further adjusted for confounders in the process (Tables 4 and 5). The results showed that only hs-CRP remained significant in the relationship between LIPC and ΔTyG-BMI after adjusting for confounders. Notably, the inflammatory marker CAR, which exhibited significance in model 2, unexpectedly lost its effect in model 3.

Intermediation model

After adjusting for confounders, the mediation model, as shown in Fig. 3, showed that hs-CRP partially mediated the effect of the LIPC intervention on TyG-BMI, and its mediating effect accounted for 24.10% of the total effect in MHD patients (Table 6).

Discussion

This study aims to evaluate the impact of LIPC intervention on IR in ESRD patients undergoing hemodialysis. In our research, the IR status of MHD patients was assessed using TyG, TyG-BMI, TG/HDL-C, and METS-IR. The results indicated that a 4-week LIPC intervention led to an improvement in the IR index compared to the control group. In addition, we found that the change values of IR index were positively correlated with the change values of hs-CRP or CAR, which is generally consistent with the results of previous studies. Thus, proceeding to our mediation modeling analysis, we found that the inflammation indicators hs-CRP or CAR played a partial mediating role in the improvement of IR index (TyG, TyG-BMI) by LIPC. This not only further supports the potential of LIPC as a treatment for IR in MHD patients but also offers new insights for exploring the pathogenesis of IR.

Insulin resistance is commonly observed in patients with MHD [21], as insulin-mediated glucose metabolism

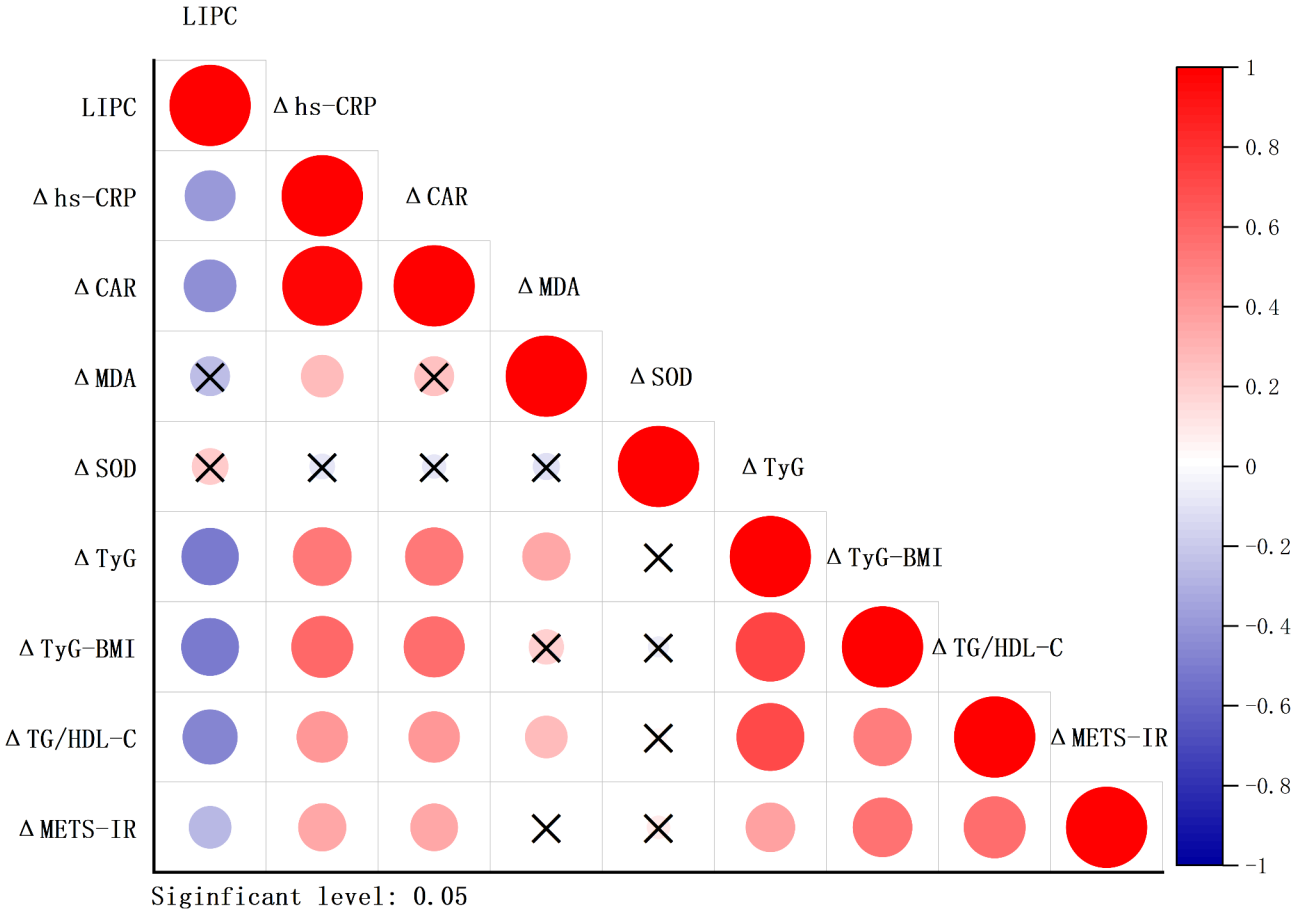

Fig. 2 Correlation between LIPC, inflammation and oxidative stress indicators and IR index
The positive correlation is red, and the negative correlation is blue. The correlation ranges from − 1 to + 1; the higher the correlation, the larger the circle. × means no association

Table 4 Sensitivity analysis with hs-CRP as a mediating variable

	model 1	model 2	model 3
ΔTyG			
total effect	(-0.63, -0.23)	(-0.6, -0.19)	(-0.48, -0.01)
direct effect	(-0.5, -0.09)	(-0.48, -0.07)	(-0.42, -0.03)
intermediary effect	(-0.27, -0.03)	(-0.26, -0.02)	(-0.22, 0.02)
ΔTyG-BMI			
total effect	(-21.36, -8.37)	(-20.18, -7.32)	(-18.04, -5.85)
direct effect	(-16.21, -3.21)	(-15.89, -3.06)	(-15.40, -2.73)
intermediary effect	(-9.37, -1.69)	(-8.66, -1.16)	(-7.73, -0.1)

Model1: unadjusted for covariates

Model2: adjusted for age, sex, BMI, glucose-lowering drugs, insulin

Model3: adjusted for age, sex, BMI, glucose-lowering medication, insulin, blood glucose, urea nitrogen, creatinine, uric acid, albumin, HDL-C, Triglyceride

The mediating effect is considered significant if the 95% confidence interval (BootLLCI-BootULCI) does not include zero

Table 5 Sensitivity analysis with CAR as a mediating variable

	model 1	model 2	model 3
ΔTyG			
total effect	(-0.63, -0.23)	(-0.6, -0.19)	(-0.48, -0.01)
direct effect	(-0.52, -0.1)	(-0.5, -0.07)	(-0.43, -0.03)
intermediary effect	(-0.26, -0.02)	(-0.25, -0.01)	(-0.22, 0.04)
ΔTyG-BMI			
total effect	(-21.36, -8.37)	(-20.18, -7.32)	(-18.04, -5.85)
direct effect	(-17.03, -3.67)	(-16.47, -3.32)	(-15.83, -2.78)
intermediary effect	(-9.03, -1.08)	(-8.11, -0.89)	(-8.00, 0.32)

Model1: unadjusted for covariates

Model2: adjusted for age, sex, BMI, glucose-lowering drugs, insulin

Model3: adjusted for age, sex, BMI, glucose-lowering medication, insulin, blood glucose, urea nitrogen, creatinine, uric acid, albumin, HDL-C, Triglyceride

The mediating effect is considered significant if the 95% confidence interval (BootLLCI - BootULCI) does not include zero

relies on the proper functioning of the downstream insulin receptor substrate (IRS)-PI3K-Akt signaling pathway. Besides, at the molecular level, cells sense insulin through the insulin receptor, and signals are propagated through a molecular cascade collectively known as phosphatidylinositol 3-kinase (PI3K) as well as the downstream protein kinase B/Akt (PKB/Akt) signaling pathway [22]. This pathway is influenced by factors related to the uremic environment, such as inflammation, acidosis, vitamin D deficiency, anemia, and the accumulation of uremic toxins [23]. In a prospective report, one mechanism linking the inflammatory response to the

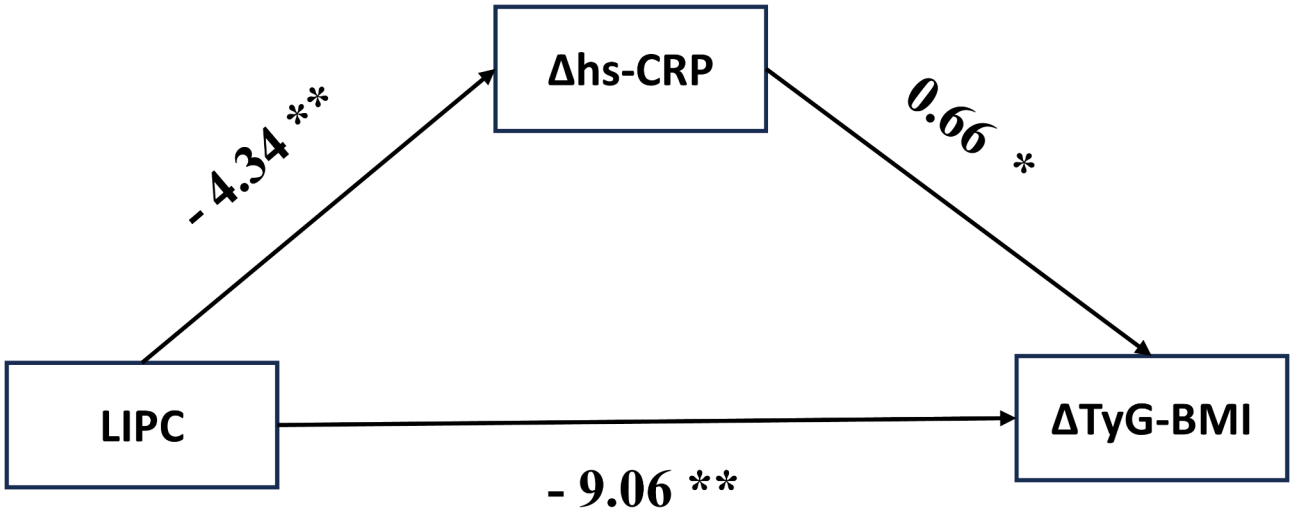

Fig. 3 Modeling of Δhs-CRP as a mediator of the effect of LIPC on ΔTyG-BMI. The presented effect size of each relationship was a standardized coefficient. The mediation effect was considered to be significant if the 95% confidence interval (CI) did not include zero, *P < 0.05, **P < 0.01. LIPC significantly affected Δhs-CRP and ΔTyG-BMI. (Coefficient = -4.34, P < 0.01; Coefficient = -9.06, P < 0.01). Δhs-CRP significantly affected ΔTyG-BMI. (Coefficient = 0.66, p < 0.05)

Table 6 Decomposition of total, direct and mediating effects in the ΔTyG-BMI mediation model

ΔTyG-BMI model effect	Effect	Boot SE	BootLLCI	BootULCI	effect size
total effect	-11.95	3.03	-18.04	-5.85	
direct effect	-9.06	3.15	-15.40	-2.73	75.82%
intermediary effect	-2.88	1.99	-7.73	-0.10	24.10%

The mediating effect is considered significant if the 95% confidence interval (BootLLCI - BootULCI) does not include zero

development of insulin resistance involves the activation of serine/threonine 'stress kinases' that may be activated in response to inflammatory cytokines. Once activated, these stress kinases impact the insulin signaling cascade by phosphorylating IRS proteins on serine residues in insulin-sensitive cells, including hepatocytes, adipocytes, and myocytes [24].

While the hyperinsulin-normoglycemic clamp is regarded as the most accurate method for measuring insulin sensitivity, its clinical use has been restricted due to its high cost and complexity [16]. Recent studies have established a connection between intrahepatic and intrapancreatic fat accumulation and IR. Hyperesterolemia may contribute to the accumulation of fatty acids in non-adipose tissues, such as the liver, muscle and heart, which in turn induces ectopic lipid deposition that is lipotoxic [18]. In addition, it has been suggested that the cause of insulin resistance is not limited to the accumulation of fat within adipose tissue per se, but may also be closely related to the inflammatory response triggered by ectopic lipid deposition. Chronic low-grade systemic inflammation impairs insulin function within the insulin signaling pathway, disrupting glucose homeostasis and resulting in widespread metabolic dysregulation [25]. Based on these insights, convenient and effective methods for assessing IR, including TyG, TyG-BMI, TG/HDL-C, and METS-IR, have been established. In particular, for the Chinese cohort, TyG and TyG-BMI showed superior sensitivities compared to TG/HDL-C ratio and METS-IR [26]. These simple, convenient, and low-cost alternatives do not require insulin dosing and can be used in all subjects regardless of their insulin treatment status [27].

IR is considered to be a central pathogenetic feature of a cluster of cardiovascular risk factors, including hypertension, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, as well as vascular stiffness [28, 29]. Endothelial dysfunction is an early manifestation of insulin resistance and plays a key role in the development of atherosclerosis [30]. To date, two models of endothelium-specific insulin receptor disruption have been reported. Vascular endothelial insulin receptor knockout mice and endothelium-specific dominant inactivating mutant insulin receptor overexpressing transgenic mice have demonstrated that intact insulin signaling in the endothelium is required for the maintenance of normal cellular function [31]. Moreover, clinical studies have demonstrated similar evidence that endothelial dysfunction is a key feature of CVD, and its associated risk factor states are also demonstrated in clinical studies [32]. In addition to endothelial dysfunction, several mechanisms may contribute to the potential causal relationship between IR and CVD. These include the promotion of oxidative stress, systemic inflammation, and the activation of the renin-angiotensin-aldosterone system [33].

Insulin is a well-recognized net protein anabolic hormone and resistance to the protein anabolic effects of insulin may be an essential factor contributing to PEW and sarcopenia in patients with MHD [34]. The various etiologies of PEW are still being refined, but the common pathways underlying all these mechanisms seem to involve increased protein degradation coupled with decreased protein synthesis [35]. PEW occurs not only due to inadequate nutritional intake in MHD patients, but also due to muscle depletion caused by inflammation, and metabolic and hormonal dysregulation, resulting in browning of adipose tissue, muscle atrophy, and increased resting energy expenditure, which ultimately leads to a severe poor prognosis for patients with MHD [36]. Additionally, the hemodialysis procedure itself is an essential factor in accelerating this process [37]. In the baseline diabetes-free cohort study, ED Siew et al. found that IR was common among patients with MHD and had a significant impact on skeletal muscle proteolysis. This association remained significant even after adjusting for various covariates. It is implied that PEW in MHD is strongly associated with IR [37]. Therefore, IR, which serves as a common risk factor for both CVD and PEW, is closely linked to poor prognosis in patients with MHD. Interventions aimed at improving IR could potentially enhance clinical outcomes and reduce mortality in this patient population.

In MHD patients, impaired endothelial function is closely associated with decreased NO bioavailability, a change that may exacerbate local inflammatory responses due to diminished NO anti-inflammatory properties. Notably, LIPC exhibited significant anti-inflammatory potential, which was exerted by efficiently blocking inflammatory signaling pathways [38]. In a rat model of myocardial infarction, A. Valtchanova-Matchouganska found that LIPC attenuated myocardial injury by inhibiting myocardial CRP production [39]. In a mouse model of sepsis-induced acute kidney injury, LIPC may exert anti-inflammatory and anti-apoptotic effects on septic AKI by inducing a systemic upregulation of miR-21 [40]. Of particular importance, this mechanism was also validated in healthy volunteers: ischemic preconditioning of the upper arm not only attenuated endothelial dysfunction in the contralateral arm, but also reduced inflammatory cell activation and suppressed the expression of pro-inflammatory genes in circulating leukocytes, achieving a teleprotective effect [41]. In an in-depth study by our group, we found that LIPC ameliorated contrast-induced acute kidney injury (CI-AKI) in mice, and the underlying mechanisms may include inhibition of mPTP opening, suppression of oxidative stress, and attenuation of inflammation through GSK-3β phosphorylation [42]. In a clinical study, by comparing it to the Sham group of MHD patients, we found significant improvements in restless legs syndrome and sleep quality scores in patients with LIPC intervention, which may be partly due to its reduction of ROS oxidation of DNA. Overall, in addition to the reduction in oxidative stress following prolonged ischemia, the LIPC group also exhibited a decrease in the inflammatory response [10]. Given that the pathogenesis of IR is closely related to inflammation and oxidative stress, LIPC has also demonstrated a positive effect in ameliorating inflammation and oxidative stress. Consequently, the main purpose of this study was to investigate whether LIPC was effective in reducing IR index in MHD patients and to further elucidate its potential mechanism of action.

Recent studies have indicated that the unifying mechanisms of insulin signaling and functional downregulation in MHD are increased inflammation and reactive oxygen species (ROS) production [31]. Furthermore, the interrelationships between inflammation and oxidative damage in the complex internal environment of MHD patients enable them to mutually activate one another [31]. For example, factors such as infections and uremic toxins can serve as triggers for this interplay. The mechanisms of action were therefore explored, and it was found that the improvement in IR indices by the LIPC intervention was, in part, mediated by the inhibition of hs-CRP. As mentioned previously, this may result from the effect of inflammation on the insulin signaling pathway. Consistent with our findings, Jin-Wen Xu et al. reported that CRP impairs insulin signaling by regulating Syk tyrosine kinase and RhoA, which in turn affects the phosphorylation of insulin receptor substrate-1, Akt, and endothelial nitric oxide synthase (eNOS) in vascular endothelial cells [30]. In addition, a recent study showed that infusion of inflammatory factors into healthy subjects directly inhibits glucose uptake and metabolism in skeletal muscle, thereby inducing insulin resistance. The underlying mechanism appears to be related to impaired phosphorylation of Akt substrate 160, leading to impaired GLUT4 translocation and glucose uptake [43]. Mengliu Yang, by constructing a CRP knockout (KO) rat model, determined that systemic reduction of CRP enabled rats to resist weight gain and insulin resistance induced by a high-fat diet and also significantly promoted energy expenditure and insulin-regulated glucose metabolism. glucose metabolism. These findings suggest that CRP is not merely an inflammation biomarker but also plays a pivotal role in regulating energy balance, body weight, insulin sensitivity, and glucose homeostasis [44]. Notably, although our study showed that LIPC was effective in reducing the levels of oxidative stress and IR, MDA and SOD did not show significant effects in the mediated effects model. This finding is at variance with our expectation because it has been widely reported in the research literature that LIPC can significantly inhibit oxidative

stress, which is usually considered as one of the key factors inducing IR [45]. We speculate that this result may be related to the small sample size.

Limitations

This study has several limitations. Firstly, we did not include the insulin resistance index HOMA-IR because of its limited value for subjects receiving insulin therapy or patients with beta cell damage. Secondly due to the retrospective study it was not possible to add new indicators such as inflammatory indicators IL-6, TNF-α. Finally, the present study still suffers from a small observational sample size without longer term interventions and follow-up to understand the development of IR in the subjects, and some of the negative results may also be related to the small sample size. Therefore, prospective, multicenter, large sample size, randomized controlled studies are needed for further confirmation.

Conclusion

IR affects the prognosis of patients with MHD. Nonetheless, the etiology of IR is multifactorial, but chronic inflammation seems to be an important factor. The present study preliminarily validates LIPC as a safe and effective method to ameliorate IR in MHD patients.

Abbreviations

MHD	Maintenance hemodialysis
CVD	Cardiovascular disease
PEW	Protein-energy wasting
IR	Insulin resistance
LIPC	Limb ischemic preconditioning
TyG	Triglyceride-glucose index
TyG-BMI	Triglyceride-glucose body mass index
TG/HDL-C	Triglyceride-to-high-density lipoprotein cholesterol ratio
METS-IR	Metabolic score of insulin resistance
hs-CRP	High-sensitivity C-reactive protein
MDA	Serum malondialdehyde
SOD	Superoxide dismutase
CKD	Chronic kidney disease
IPC	Ischemic preconditioning
RLS	Restless Legs Syndrome
ELISA	Enzyme-linked immunosorbent assay
BMI	Body mass index

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Author contributions

YZ, YT and LX contributed conception and design of the study. LF, XL and WM organized the database. YZ performed the statistical analysis. YZ and YT wrote the first draft of the manuscript. LX and TL revised the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Changzhou Second People's Hospital affiliated with Nanjing Medical University ([2023]KY213-01). All methods were performed in accordance with relevant guidelines and regulations. Patient information was kept confidential and no information that could lead to patient identification was included in the study. The signing of informed consent is exempted: according to the Measures for Ethical Review of Biomedical Research Involving Human Beings, research using human materials or data with identifiable information can no longer be found in the subjects, and the research project does not involve personal privacy or commercial interests. The requirement for informed consent is waived because the research is retrospective in nature. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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