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The Interplay of Systemic Inflammation and Oxidative Stress in Connecting Perirenal Adipose Tissue to Hyperuricemia in Type 2 Diabetes Mellitus: A Mediation Analysis

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Background: Emerging evidence suggests that increased perirenal adipose tissue (PAT) may trigger systemic inflammation and oxidative stress, potentially contributing to hyperuricemia (HUA). This study aimed to explore the link between PAT and HUA risk, and the potential mediating role of inflammation and oxidative stress.

Methods: This study recruited 903 participants with T2DM. Monocyte to high-density lipoprotein cholesterol ratio (MHR) was computed to assess systemic inflammation and oxidative stress. Perirenal fat thickness (PrFT) was measured by unenhanced abdominal CT, indicating PAT mass. Weighted binomial logistic regression analysis and restricted cubic splines (RCS) analyses were employed to analyze the association correlation of HUA risk with PrFT and MHR. Meanwhile, adjusted mediation analysis based on bootstrapping calculations was performed to evaluate the direct impact of PrFT on HUA risk and the indirect effect mediated by MHR.

Results: Participants in the HUA group exhibited markedly higher levels of PrFT and MHR than the non-HUA group ($P < 0.001$). Serum uric acid presented a positive correlation with PrFT (β=0.368, P<0.001) and MHR (β=0.188, P<0.001) following adjustments for confounding factors. PrFT and MHR demonstrated an independent association with HUA risk after full adjustment for confounding factors in Model 3, with the ORs (95% CI) at 1.24 (95% CI:1.19–1.30, P<0.001) and 1.32 (95% CI:1.14–1.53, P<0.001), respectively. RCS analysis confirmed a non-linear association between PrFT, MHR, and HUA risk (P for nonlinear and overall< 0.001). Furthermore, MHR accounted for a mediated proportion of 11.29% in this association (P<0.001).

Conclusion: Increased PAT was an independent factor in HUA risk, with systemic inflammation and oxidative stress mediating this relationship.

Keywords: perirenal adipose tissue, systemic inflammation and oxidative stress, hyperuricemia, perirenal fat thickness, monocyte to high-density lipoprotein cholesterol ratio

Introduction

Hyperuricemia (HUA), the primary cause of gout, is increasingly prevalent due to lifestyle changes and rising obesity rates. Obesity, delineated by the accretion of excessive visceral and subcutaneous adipose tissue, emerges as a pivotal catalyst in the global type 2 diabetes mellitus (T2DM) and HUA pandemic. The metabolic repercussions of obesity exhibit marked heterogeneity across distinct phenotypes, with visceral adiposity showcasing a closer association with HUA, as opposed to its subcutaneous counterpart,[1] indicating the pivotal role ascribed to visceral adipose tissue (VAT) in the pathogenesis of HUA. Perirenal adipose tissue (PAT), a subtype of VAT, has recently attracted clinical insights due to its unique metabolic and cardiovascular ramifications.[2,3] Perirenal fat thickness (PrFT) measured by computed tomography has been validated as a reliable index assessing PAT mass.[4] In addition, some clinical studies also revealed that PrFT and PAT volume were independently correlated with serum uric acid (UA) levels after adjusting for confounding

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factors,[5,6] indicating a potential role in HUA. T2DM is particularly susceptible to associated with HUA, a condition that significantly elevates the risk of cardiovascular disease, metabolic syndrome, chronic kidney disease,[7] and overall mortality.[8] Given the high prevalence of HUA and its associated complications, understanding the role of PAT in HUA can help develop more targeted and effective strategies to reduce the risk of these serious outcomes in T2DM. However, few studies have explored the association between PAT accumulation and HUA.

UA is a crucial substance that plays a significant role in metabolism and various physiological processes. It possesses multiple properties, including oxidative, antioxidant, and anti-inflammatory capabilities, contributing to its importance in the body. Recent studies have suggested that the body may compensate for the rise of chronic low-grade inflammation and oxidative stress through various mechanisms, possibly including the actions of UA.[9] Furthermore, emerging evidence suggests that excessive hypoxia caused by PAT can trigger lipolysis, leading to a significant increase in immune cell components in adipose tissue regions and a rise in the local synthesis of pro-inflammatory cytokines.[10] These findings support the well-known properties of PAT to induce systemic inflammation and oxidative stress. Limited data are investigating the role of systemic inflammation and oxidative stress on the association between PAT and HUA. In previous studies, the monocytes to high-density lipoprotein cholesterol ratio (MHR) has been validated as a simplicity and cost-effectiveness marker of inflammation and oxidative stress.[11–13] To further discover the complex interplay between PAT, systemic inflammation, oxidative stress, and HUA. This study mainly aimed to evaluate the correlation of HUA with PrFT and MHR and investigate whether MHR mediates the association between PrFT and HUA in T2DM.

Methods

Participants and Study Design

This cross-sectional study collected data from the National Metabolic Management Center at Longyan First Affiliated Hospital of Fujian Medical University, recruiting participants with T2DM admitted between August 2022 and January 2024. Written informed consent was obtained from all participants following ethical guidelines set by the Ethical Committee of Longyan First Affiliated Hospital of Fujian Medical University (IC-2022-009). The study adhered to the principles of the Declaration of Helsinki throughout. Inclusion criteria for the study were as follows: 1) A confirmed diagnosis of T2DM) based on the World Health Organization 2019 diagnostic criteria. 2) Age $\geq$ 18 years and willingness to provide informed consent and participate in the study. Exclusion criteria were meticulously enforced to ensure the judicious selection of participants. Specifically, individuals were excluded if they presented with any of the following conditions that could potentially confound monocyte count (eg, acute or chronic infections, acute stress states, anemia, hemolytic diseases, and bleeding), influence UA levels (eg, malignant tumors, pregnancy, renal dysfunction, severe heart failure, and concurrent administration of medications such as anti-hyperuricemic agents, diuretics, glucocorticoids, and sodium-glucose cotransporter-2 inhibitors), renal abnormalities (eg, renal or perirenal neoplasms, cysts, and a history of renal region surgery), inability to undergo CT scanning (eg, pregnancy or severe spinal curvature), and incomplete data. This study estimated the sample size based on the requirements for a weighted binomial logistic regression model. According to the rule of thumb of 10–15 events per variable, and considering that the prevalence of HUA in T2DM is approximately 30%, we calculated that a sample size of 800–900 participants would be necessary to adequately account for 12–18 potential variables in the model. Consequently, 903 participants were included in the final analysis, categorized into HUA (n=316) and non-HUA (n=587) groups.

Clinical and Laboratory Assessments

Demographic data, including gender, age, diabetic duration, medication history, comorbidities, and lifestyle habits such as smoking and alcohol consumption, were meticulously gathered by the proficient physician. This comprehensive information was obtained through structured questionnaires and a thorough examination of medical records and laboratory findings. Anthropometric measurements, encompassing height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP), were meticulously acquired by trained research nurses at the Metabolic Management Center following standardized protocols to ensure accuracy and reliability.

Blood samples were collected from participants following a minimum 8-hour fasting period for comprehensive laboratory analysis. This analysis covered a range of biochemical parameters including creatinine, alanine aminotransferase, UA, fasting plasma glucose (FBG), serum insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), as well as hemoglobin A1c (HbA1c) and monocyte count. These biochemical parameters were assessed using an auto-biochemical analyzer (Roche Diagnostics Corporation). Monocyte count was determined utilizing the Coulter LH 780 Analyzer (Beckman Coulter Ireland, Galway, Ireland), while HbA1c levels were assessed through high-performance liquid chromatography with a D10 set (Bio-Rad).

Exposure Variable Assessment

In the present study, PrFT serves as the primary exposure variable, validated as a reliable estimate of PAT mass.[4] Two seasoned radiologists meticulously performed PrFT measurements following standardized protocols. Initially, Participants underwent unenhanced abdominal CT scans from the pubic symphysis to the 10th thoracic vertebra to capture renal and perirenal structural details. PAT was distinguished from surrounding tissues utilizing density criteria (window center: −100 hU; widths: −50 to −200 hU). Subsequently, PAT was defined as the distance from the kidney to the nearest visceral or muscular structure. Finally, PrFT was assessed as the average maximum distance from the posterior renal wall to the inner edge of the abdominal wall along the plane delineated by the left and right renal veins. The inter-operator agreement between the two radiologists is 0.93.

Assessment of Mediator and Outcome Variable Definition

In the present study, MHR serves as the mediator, recognized as a marker of systemic inflammation and oxidative stress. The MHR was calculated using the formula: MHR = (monocyte count) / (HDL-c level). HUA was designated as the outcome variable, diagnosed according to the latest Chinese practice guideline for patients with hyperuricemia/gout: on two separate occasions, participants with fasting UA levels exceeding 420 μmol/L.[14]

Study Covariates

Three models were constructed to control for potential confounding variables influencing the association between PrFT and HUA. Model 1 included adjustments for age, gender, diabetic duration, smoking, drinking habits, and hypertension. Model 2 incorporated adjustments for body mass index (BMI), WC, creatinine, ALT, HbA1c, TG, TC, LDL-c, and homeostatic model assessment of insulin resistance (HOMA-IR). Model 3 was adjusted for visceral fat area (VFA) and subcutaneous fat area (SFA). BMI was computed as weight (kg) divided by the square of height (m^2). HOMA-IR was determined by the formula: fasting serum insulin (μU/mL) multiplied by FBG (mmol/L), divided by 22.5. Trained operators measured VFA and SFA using a dual bioelectrical impedance analyzer (DUALSCANHDS-2000, Omron Healthcare Company, Japan).

Statistical Analysis

Baseline characteristics of the study cohort were presented as means ± standard deviation (SD) for continuous variables, while categorical variables were expressed as frequency tables (N, %). Differences between the HUA and non-HUA groups were assessed using Student's *t*-test or the chi-square test. The correlation between UA levels and MHR and PrFT was examined via Spearman correlation analysis. Subsequently, these correlations were further analyzed using weighted multiple regression analysis after adjusting for confounding factors. Additionally, the relationship between HUA risk and MHR and PrFT was investigated using weighted binomial logistic regression analysis and Restricted cubic splines (RCS), with adjustment for relevant confounders across different models. Furthermore, the adjusted mediation analysis based on bootstrapping calculations was employed to evaluate the direct impact of PrFT on HUA risk and the indirect effect mediated by MHR. To further strengthen the robustness of our study findings and account for potential variations in MHR. Sensitivity analyses were performed, specifically focusing on the associations mentioned above in the subgroup of women. All statistical analyses were performed using R language 4.2.3 software, with significance set at $P < 0.05$ (two-tailed).

Result

Baseline Characteristics of the Study Population Based on HUA Statutes

In the final analysis, this study encompassed 903 individuals with T2DM, among whom 403 (50.5%) were male, averaging 54.7±8.2 years in age, with a prevalence of HUA at 34.9%. Table 1 summarizes the detailed overview of baseline characteristics of the study population based on HUA statutes. In contrast to the non-HUA group, participants in the HUA group not only demonstrated increased metabolic parameters like WC, BMI, SBP, DBP, TG, HOMA-IR, monocytes, VFA, and SFA but also displayed reduced levels of HDL-c ($P < 0.05$). Additionally, the distribution of MHR and PrFT according to HUA statutes is presented in Figure 1. The results revealed that participants in the HUA group exhibited markedly higher levels of PrFT and MHR than the non-HUA group ($P < 0.001$).

Associations Among UA, PrFT, and MHR

Figure 2 illustrates the correlation of UA with PrFT and MHR analyzed by the Pearson correlation analysis. The results indicated that UA was positively correlated with PrFT ($r = 0.545$, $P < 0.001$) and MHR ($r = 0.466$, $P < 0.001$). Furthermore, a positive association between PrFT and MHR was observed ($r = 0.376$, $P < 0.001$). Subsequently, multiple linear regression analysis was further conducted to evaluate these correlations after adjustment for confounding factors (Table 2). In Model 1 and Model 2, PrFT and MHR exhibited a positive correlation with UA. Similarly, a positive association between PrFT and MHR was observed. Additionally, with the full adjustments in Model 3, UA maintained significant correlations with PrFT (β=0.368, P<0.001) and MHR (β=0.188, P<0.001). Additionally, PrFT demonstrated a positive association with MHR (β=0.176, P<0.001).

Table 1 Comparison of Clinical Characteristics Between HUA and Non-HUA Groups

Variable	Total (n=903)	HUA (n=316)	Non-HUA (n=587)	*P* value
Age (year)	54.7±8.2	54.8±7.9	54.6±8.3	0.802
Male, n (%)	483 (50.5)	161 (50.9)	291 (49.6)	0.693
Diabetic duration (year)	7.8±3.2	7.7±3.1	7.9±3.3	0.574
BMI (kg/m^2)	24.1±3.1	25.6±2.6	23.3±2.9	<0.001
WC (cm)	85.2±7.0	88.4±6.5	83.4±6.6	<0.001
SBP (mmHg)	132.6±18.2	143.7±12.4	126.6±18.1	<0.001
DBP (mmHg)	80.2±9.2	84.4±10.3	78.2±8.2	<0.001
HbA1c (%)	8.82±1.06	8.77±0.87	8.84±1.15	0.339
TG (mmol/L)	2.17±1.37	2.85±1.42	1.80±1.19	<0.001
TC (mmol/L)	5.28±1.18	5.31±1.27	5.29±1.14	0.752
HDL-c (mmol/L)	1.08±0.23	0.97±0.16	1.16±0.25	<0.001
LDL-c (mmol/L)	3.54±0.93	3.53±0.99	3.52±0.91	0.880
Creatinine (umol/L)	69.1±13.4	69.7±13.3	68.7±12.8	0.261
ALT (IU/L)	39.6±8.7	39.4±9.7	39.8±8.3	0.579
Monocyte (10^8/L)	4.15±1.00	4.53±0.95	3.94±1.01	<0.001
HOMA-IR	3.08±1.77	3.80±1.53	2.69±1.72	<0.001
VFA (cm^2)	83.4±32.0	89.1±29.4	80.4±32.2	<0.001
SFA (cm^2)	170.1±40.1	176.2±42.4	166.8±41.2	<0.001
Hypertension, n (%)	319 (35.3)	135 (42.7)	138 (23.5)	<0.001
Smoking, n (%)	280 (31.0)	91 (28.8)	189 (32.2)	0.292
Drinking, n (%)	320 (35.4)	137 (43.2)	183 (31.2)	<0.001

Abbreviations: BMI, body mass index; WC, waist circumference; HbA1c, Glycated hemoglobin; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMR-IR, homeostasis model assessment insulin resistance; ALT, alanine aminotransferase; VFA, visceral fat area; SFA, subcutaneous fat area; MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; UA, uric acid; HUA, hyperuricemia.

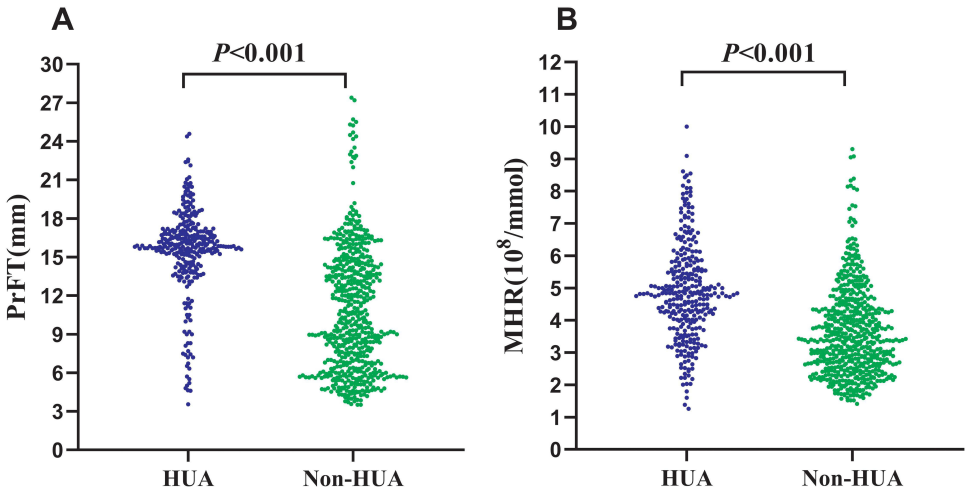

Figure 1 Distribution of PrFT (**A**) and MHR (**B**) between the HUA group and non-HUA group. MHR: monocyte to high-density lipoprotein cholesterol ratio.
Abbreviations: PrFT, perirenal fat thickness; HUA, hyperuricemia.

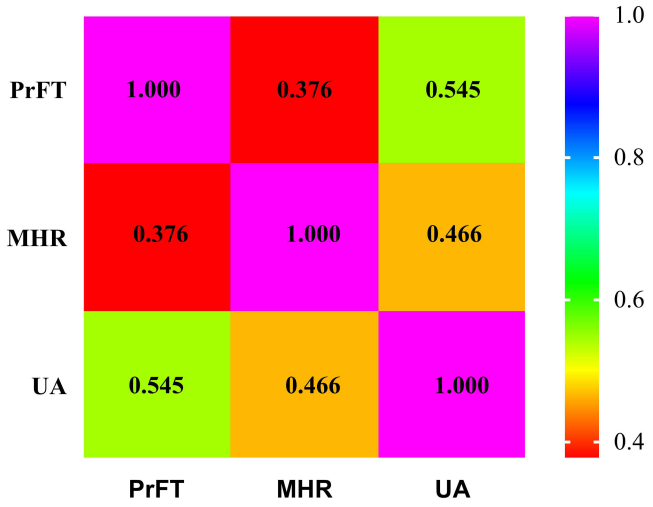

Figure 2 Pearson correlation analysis of the association among PrFT, MHR, and UA.
Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; UA, uric acid.

Association Between PrFT, MHR, and HUA Risk

Table 3 displays the findings of the association between PrFT, MHR, and HUA risk after applying adjustments through 3 models analyzed by the weighted binomial logistic regression. The findings highlighted that higher PrFT and MHR quartiles were positively correlated with increased HUA risk compared to the first quartile, across all three models

Table 2 Weighted Multivariate Linear Regression Analysis for the Independent Associations Among PrFT, MHR, and UA

Independent variables	Dependent variables	Model 1		Model 2		Model 3	
		β	*P*	*β*	*P*	*β*	*P*
PrFT	UA	0.465	<0.001	0.400	<0.001	0.368	<0.001
MHR	UA	0.364	<0.001	0.220	<0.001	0.188	<0.001
MHR	PrFT	0.342	<0.001	0.285	<0.001	0.176	<0.001

Notes: Model 1: adjusted for age, gender, diabetic duration, smoking, drinking, and hypertension. Model 2: adjusted for body mass index, waist circumference, glycated hemoglobin A1c, triglyceride, alanine aminotransferase, creatinine, total cholesterol, low-density lipoprotein cholesterol, and homeostasis model assessment insulin resistance. Model 3: additionally adjusted for visceral fat area and subcutaneous fat area.
Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; UA, uric acid.

Table 3 Weighted Binomial Logistic Regression Analysis for the Correlations of PrFT and MHR with HUA Risk

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PrFT (mm)						
Per SD increase	4.32(2.41–7.76)	<0.001	2.87(2.33–3.53)	<0.001	2.66(1.85–3.89)	<0.001
Overall	1.31(1.22–1.40)	<0.001	1.26(1.18–1.34)	<0.001	1.24(1.19–1.30)	<0.001
Q1	Ref. (1.0)		Ref. (1.0)		Ref. (1.0)	
Q2	2.32(1.36–3.95)	0.002	1.93(1.11–3.35)	0.020	1.83(1.05–3.19)	0.003
Q3	5.76(3.45–9.63)	<0.001	4.07(2.34–7.09)	<0.001	3.81(2.18–6.65)	<0.001
Q4	7.36(4.31–12.56)	0.002	4.15(2.23–7.73)	<0.001	3.96(2.13–7.39)	<0.001
P for trend	<0.001		<0.001		<0.001	
MHR (10^8/L)						
Per SD increase	1.93(1.44–2.60)	<0.001	`1.56(1.24–1.96)	<0.001	1.53(1.22–1.93)	<0.001
Overall	1.57(1.39–1.77)	<0.001	1.36(1.17–1.58)	<0.001	1.32(1.14–1.53)	<0.001
Q1	Ref. (1.0)		Ref. (1.0)		Ref. (1.0)	
Q2	1.39(1.10–1.74)	0.005	1.35(1.12–1.62)	0.002	1.26(1.04–1.52)	0.019
Q3	2.18(1.51–3.16)	<0.001	1.96(1.22–3.16)	0.006	1.56(1.34–1.81)	<0.001
Q4	4.37(2.57–7.44)	<0.001	2.34(1.60–3.44)	<0.001	1.98(1.35–2.90)	<0.001
P for trend	<0.001		<0.001		<0.001	

Notes: Model 1: adjusted for age, gender, diabetic duration, smoking, drinking, and hypertension. Model 2: adjusted for body mass index, waist circumference, glycated hemoglobin A1c, alanine aminotransferase, creatinine, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and homeostasis model assessment insulin resistance. Model 3: additionally adjusted for visceral fat area and subcutaneous fat area.

Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; HUA, Hyperuricemia.

(*P*<0.05). Meanwhile, PrFT and MHR demonstrated an independent association with HUA risk after full adjustment for confounding factors in Model 3, with the ORs (95% CI) at 1.24 (95% CI:1.19–1.30, *P*<0.001) and 1.32 (95% CI:1.14–1.53, *P*<0.001), respectively. Similarly, each standard deviation (SD) increase in PrFT and MHR caused a 166% and 53% additional risk for HUA (*P*<0.05). The findings also revealed a significant dose-response relationship between PrFT, MHR, and HUA risk (*P*<0.001). Notably, Figure 3 depicts the results of the RCS analysis examining these associations after adjusting for Model 3. The findings confirm a non-linear association between PrFT, MHR, and HUA risk (*P* for nonlinear and overall< 0.001).

Mediating Role of MHR

Figure 4 provides the results derived from the adjusted mediation analysis, exploring the mediating role of MHR in the association between PrFT and HUA risk, following adjustments for confounding variables. In Model 1, the total and indirect effects of PrFT on HUA risk were 0.511 and 0.128, respectively. Notably, MHR contributed to a mediated proportion of 25.04% in this association (*P*<0.001). Subsequently, Model 2, incorporating adjustments for metabolic profiles, observed reductions in total and direct effects to 0.352 and 0.050, respectively. Concurrently, the mediated proportion declined to 14.20% (*P*<0.001). Remarkably, in Model 3, where further adjustments for VFA and SFA were applied, the total and direct effects were decreased to 0.301 and 0.034. Meanwhile, the mediated proportion of MHR decreased to 11.29% while remaining statistically significant (*P*<0.001).

Sensitivity Analysis

Sensitivity analyses were performed within a subgroup of women to evaluate the abovementioned associations. The results demonstrated consistent findings in Supplementary Table 1 and Supplementary Figure 1. In the fully adjusted

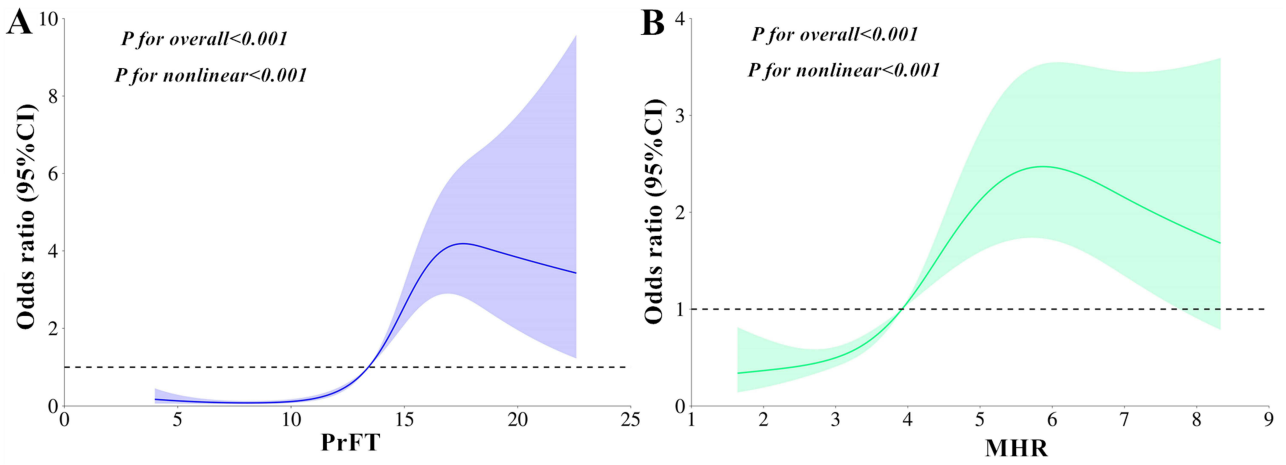

Figure 3 Restricted cubic splines analysis for the correlation of HUA risk with PrFT (**A**) and MHR (**B**) in Model 3. MHR: monocyte to high-density lipoprotein cholesterol ratio. Model 3 adjusted age, gender, diabetic duration, smoking, drinking, hypertension, body mass index, waist circumference, creatinine, alanine aminotransferase, glycated hemoglobin A1c, triglyceride, total cholesterol, low-density lipoprotein cholesterol, homeostasis model assessment insulin resistance, visceral fat area, and subcutaneous fat area.

Abbreviations: PrFT, perirenal fat thickness; HUA, hyperuricemia.

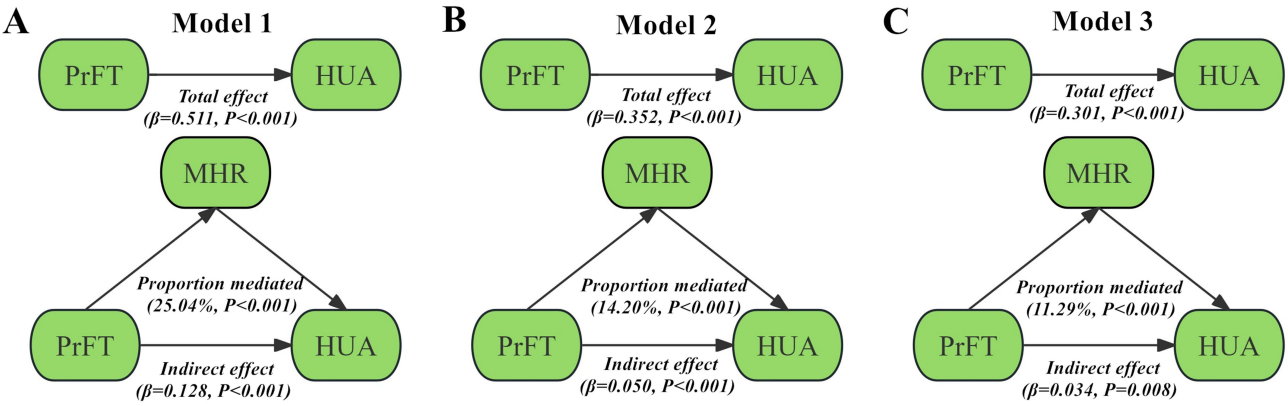

Figure 4 Structural model for the mediating role of MHR in the association between PrFT and HUA in Model 1 (**A**), Model 2 (**B**), and Model 3 (**C**). Model 1: adjusted for age, gender, diabetic duration, smoking, drinking, and hypertension. Model 2: adjusted for body mass index, waist circumference, creatinine, alanine aminotransferase, glycated hemoglobin A1c, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and homeostasis model assessment insulin resistance. Model 3: additionally adjusted for visceral fat area and subcutaneous fat area.

Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; HUA, hyperuricemia.

Model 3, UA exhibited a positive correlation with PrFT (β=0.251, P<0.001) and MHR (β=0.181, P<0.001). Likewise, a positive association between PrFT and MHR was observed (β=0.164, P<0.001). Furthermore, PrFT and MHR represented independent variables for hyperuricemia, with odds ratios of 1.54 (95% CI: 1.28–1.82, P<0.001) and 1.29 (95% CI: 1.05–1.58, P=0.012), respectively. Additionally, the total and indirect effects of PrFT on HUA risk were 0.356 and 0.036, as depicted in Supplementary Figure 2. Notably, MHR revealed a mediated proportion of 10.1% in this association (P<0.001).

Discussion

This study prospectively enrolled 904 participants with T2DM and conducted an adjusted mediation analysis to evaluate the role of systemic inflammation and oxidative stress in the association between increased PAT and HUA. The results revealed several notable findings. Firstly, PrFT and MHR presented a positive correlation with UA following adjustments for confounding factors. Secondly, PrFT and MHR displayed an independent association with HUA risk. Thirdly, MHR partially mediated the association between PrFT and HUA. Lastly, sensitivity analysis yielded consistent results in women.

As a reliable index reflecting the PAT volume, PrFT has been utilized in various studies to investigate the relationship between increased PAT and metabolic and cardiovascular disorders. Previous research by Wang et al and Guo et al demonstrated that elevated PrFT was an independent predictor and a significant diagnostic marker of metabolic syndrome.[15,16] Additionally, Yang et al showed an independent association between PrFT and the presence and advanced fibrosis risk of non-alcoholic fatty liver disease.[17] Furthermore, several studies have indicated a close association between PrFT and DM-related disorders. Large cohort studies found that PrFT was independently associated with a higher incidence of chronic kidney disease (hazard ratio 1.67, 95% CI 1.04–2.68) in DM.[18] Similarly, Xu et al and Shen et al observed that increased PrFT contributed to an independent variable associated with reduced glomerular filtration rate and elevated urine albumin excretion rate in T2DM.[19,20] Our previous studies also revealed a positive association between PrFT and carotid intima-media thickness in T2DM.[21] Additionally, PrFT also presented a close correlation with metabolic dysfunctions like hypertension,[22] hyperlipidemia,[23] and insulin resistance[24] in previous studies. Some observational studies observed a positive association between PrFT and UA after adjustments for confounding factors,[5] but limited research has evaluated the relationship between PrFT and HUA. Consistent with the above studies, this study also demonstrated a positive association between PrFT and UA. Previous studies revealed an autonomous correlation between HUA and visceral adiposity-related indices. Maloberti et al demonstrated that lipid accumulation products are strongly associated with HUA, showing a high odds ratio OR for this relationship, based on the Uric Acid Right for Heart Health study's established cut-off value for HUA.[25] Li et al established a significant positive association between VFA and HUA in non-obese adults, with this relationship remaining statistically significant when stratified by sex.[26] Consistent with the above studies, PrFT displayed an independent association with HUA risk, even after adjusting for SFA, VFA, and other confounding factors suggested in previous studies. These findings indicated that PAT plays a vital role in the pathogenesis of HUA and may serve as a potential target for managing HUA.

UA serves as the final product of purine catabolic metabolism and plays a crucial role in human metabolism and various physiological processes. Elevated UA can damage cells and tissues by triggering a complex pro-inflammatory cascade and oxidative stress that promotes the expression of inflammatory proteins.[27] The clinical studies observed an increase in superoxide dismutase, interleukin-6, and tumor necrosis factor-α (TNF-α) in the HUA group than in the healthy control group, indicating inflammation and oxidative stress play key roles in developing HUA.[28] Previous studies have discovered some simplicity and cost-effectiveness markers for inflammation and oxidative stress like MHR, neutrophil to HDL ratio, lymphocyte to HDL ratio, and platelet to HDL ratio. Compared with other inflammation and oxidative stress makers, the MHR has been applied to studies evaluating the association between inflammation, oxidative stress, HUA, and UA. Li et al found a positive association between MHR and serum UA levels after adjusting confounders.[29] In addition, Chen et al demonstrated a positive relationship between MHR and prevalent HUA among rural Chinese adults.[30] Thus, this study employed MHR as a marker of inflammation and oxidative stress. This study also revealed a similar finding to the above research, MHR was positively correlated with UA (β=0.188, P<0.001) and demonstrated an independent association with HUA risk after full adjustment for confounding factors. Especially, each SD increase in MHR caused a 53% additional risk for HUA. These findings further confirmed the role of inflammation and oxidative stress in the pathological development of HUA.

Mounting evidence indicates a complex interaction involving inflammation, oxidative stress, and PAT.[31] Sharing the underlying developmental origin with typical VAT, PAT assumes a similar role to VAT in instigating various signals capable of eliciting an inflammatory response.[32] The proximity of PAT to the kidney is attributed to its specific anatomical features, such as a comprehensive vascular supply, lymphatic system, and innervation.[33] These characteristics render PAT more actively engaged in processes related to energy metabolism, as well as the synthesis and secretion of several adipokines and inflammatory cytokines. PAT demonstrates an immunoregulatory phenotype, responding to various inflammatory cytokines such as interleukin-1β, interferon, and TNF-α, potentially contributing to systemic inflammation.[34] Furthermore, PAT encompasses distinct populations of dormant unilocular and multilocular UCP1-expressing adipocytes,[35] the accumulation of PAT mass leads to increased expression levels of UCP1, exacerbating local hypoxia and increasing HIF-1α expression in the hypertrophied tissue through aberrant oxygen consumption, thus driving oxidative stress.[36] Previous studies have indicated that the organism may react to chronic low-grade inflammation and oxidative stress by elevating serum UA levels.[9,37,38] It can be speculated that the impact of increased PAT mass on

HUA may achieved in part by promoting inflammation and oxidative stress. Important aspects concerning PAT's predisposition to oxidative stress, inflammation, and its effects on HUA must be clarified. Monocytes, a key component of the immune response, play a role in the inflammatory processes that contribute to VAT accumulation. At the same time, HDL has anti-inflammatory properties that can counterbalance the pro-inflammatory effects of monocytes.[39,40] The interplay between these two components in MHR may provide insight into the systemic inflammation underlying PAT and HUA. The findings derived from the adjusted mediation analysis support this assumption. MHR partially mediated the association between PrFT and HUA. These associations remained statistically significant even after adjusting metabolic profiles and VFA.

Strength and Limitation

The notable strength of this study lies in initially corroborating the involvement of inflammation and oxidative stress in the link between increased PAT mass and HUA through mediation analysis, which was subsequently supported by sensitivity analysis. However, several limitations should be acknowledged. Firstly, the data used in this analysis were cross-sectional, constraining our capacity to establish causality or evaluate temporal relationships. Secondly, the diagnostic criteria for HUA were based on the Chinese clinical guidelines. Further investigations are warranted to explore these associations using alternative diagnostic criteria for HUA. Finally, the distribution of PAT varies among different races. Despite being a regional medical center catering to approximately three million people of Asian descent, conducting multicenter studies involving other races would enhance the robustness of our findings.

Conclusion

In conclusion, this study revealed that PrFT and MHR were independently associated with HUA risk. Furthermore, MHR was found to partially mediate the association between PrFT and HUA. These findings suggest that the impact of increased PAT on the HUA risk may achieved in part by promoting inflammation and oxidative stress. Consequently, PAT could potentially serve as a promising target for managing HUA.

Abbreviations

ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; HUA, hyperuricemia; HDL-c, high-density lipoprotein cholesterol; HOMR-IR, homeostasis model assessment insulin resistance; HbA1c, Glycated hemoglobin; LDL-c, low-density lipoprotein cholesterol; MHR, monocyte to high-density lipoprotein cholesterol ratio; PrFT, perirenal fat thickness; PAT, perirenal adipose tissue; SFA, subcutaneous fat area; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; UA, uric acid; VAT, visceral adipose tissue; VFA, visceral fat area; WC, waist circumference.

Data Sharing Statement

Datasets are available from the corresponding author Xiu Li Guo upon reasonable request.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Ethical Committee of Longyan First Affiliated Hospital of Fujian Medical University (IC-2022-009). Written informed consent was obtained from all patients/participants to participate in the study.

Consent for Publication

All participants have consented to the submission of the data to the journal.

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Disclosure

The authors report no conflicts of interest in this work.

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