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Adipokine isthmin-1 is a potential predictor of abnormal urine Na^+ excretion and insulin resistance for primary hypertension

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Abstract

Background Isthmin-1 (ISM1) plays an important role in maintaining glucose homeostasis and lipid metabolism. However, the relationship between circulating ISM1 and hypertension remains unclear. This study was aimed to investigate the association between serum ISM1 levels and blood pressure and evaluate value of circulating ISM1 for predicting abnormal Na^+ excretion and insulin resistance.

Methods Four hundred sixty-eight individuals newly diagnosed with primary hypertension and 582 healthy individuals were initially screened. 84 participants were eligible for this case–control study. Serum ISM1 levels were assessed using ELISA. Spearman correlation analysis and partial correlation analysis were conducted to confirm the correlation. Multiple linear regression analysis was used to assess the independent association of serum ISM1 concentration with blood pressure. The receiver operating characteristic (ROC) curve was employed to evaluate the sensitivity of ISM1 in predicting abnormal Na^+ excretion and insulin resistance in hypertensive subjects.

Results The serum ISM1 levels of hypertensive individuals were higher than that of healthy individuals. ISM1 levels were positively associated with systolic blood pressure (SBP), diastolic blood pressure (DBP) and brachial-ankle pulse wave velocity, but negatively associated with nocturnal urine Na^+ concentration and excretion. These associations remained significant even after adjusting for age, body mass index, sex, heart rate, glucose, total cholesterol and estimated glomerular filtration rate. Multiple linear regression analysis revealed that SBP was an independent factor associated with serum ISM1 levels. The area under receiver operating characteristic curve (AUROC) for predicting low urine Na^+ excretion and insulin resistance were 0.873 and 0.740, respectively.

Conclusions Serum ISM1 levels were positively associated with SBP and DBP. ISM1 may serve as a potential biomarker of abnormal urine Na^+ excretion and insulin resistance in primary hypertensive individuals.

Trial registration Registered on chictr.org.cn 18/04/2024 (Registration number: ChiCTR2400083204).

Keywords Adipokine, Isthmin-1, Hypertension, Renal Na^+ excretion, Insulin resistance

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Introduction

Hypertension is a prevalent metabolic disorder worldwide [1]. The number of hypertensive subjects aged 30–79 years doubled from 1990 to 2019, and most of the increase occurred in low- and middle-income regions [2]. In China, hypertension prevalence has notably risen over the past three decades, affecting approximately a quarter of Chinese adults [3]. Uncontrolled systolic blood pressure alone contributes to over 10 million annual deaths [4].

Insulin resistance and abnormal lipid metabolism pose increased risks for individuals with hypertension [5, 6]. Adipose tissue produces adipokines, which include multifunctional proteins recently implicated in hypertension, diabetes and metabolic disease [7–11]. Isthmin, a progenitor of a novel family of secreted proteins found in Xenopus embryos, exhibits robust maternal expression during embryonic development [12]. Isthmin-1 (ISM1) belongs to isthmin gene family that contains ISM1 and ISM2. ISM1 is widely distributed in different organs and involved in metabolism diseases, while ISM2 is mainly expressed in the placenta [13]. Significantly, ISM1 is considered as an adipokine that plays dual roles in increasing adipocyte glucose uptakes in adipocytes and suppressing hepatic lipid synthesis [14]. Besides, clinical trials have linked serum ISM1 levels to physiological or pathological conditions such as gestational diabetes mellitus, diabetic nephropathy, obesity and angiogenesis [15–17], indicating its possible role in metabolic diseases. However, the role of ISM1 in hypertension remains unclear; especially, population-based evidence on the relationship between serum ISM1 levels and blood pressure are still lacking.

A few studies have reported that serum ISM1 is correlated with some indicators such as high-density lipoprotein cholesterol (HDL-C) [18] and albuminuria [19] in patients with type 2 diabetes mellitus (T2DM). Moreover, serum isthmin-1 is a potential biomarker for metabolic dysfunction associated fatty liver disease in patients with metabolic syndrome and T2DM [20]. Hypertension is also recognized as a metabolic disease [21] and associated with several adipokines [8, 10, 11]. Therefore, we hypothesized that serum ISM1 may be associated with insulin resistance and blood pressure in primary hypertensive individuals. This current study aimed to investigate serum ISM1 levels and evaluate its potential utility in predicting abnormal renal Na^+ excretion and insulin resistance in hypertensive subjects.

Material and methods

Study design and data collection

This case–control study was approved by Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University and registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2400083204, 18/04/2024). Written informed consents were obtained from all participants. The study recruited participants who were newly diagnosed with hypertension according to the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg measured in the hospital examination room [22]. Blood pressure was measured three times on separate occasions. Eligible participants were aged 18–80 years. A total of 468 individuals with newly diagnosed essential hypertension and 582 control subjects were initially screened. Exclusion criteria included diabetes mellitus, secondary hypertension, chronic kidney disease, asthma, chronic obstructive pulmonary disease, acute infectious diseases, cancer, and conditions requiring long-term medication. Based on these criteria, 38 individuals with newly diagnosed essential hypertension and 46 control subjects with normal blood pressure were enrolled (Fig. 1). It should be noted that our current study was a non-matched case–control study. All participants were of Han nationality.

Measurements of serum ISM1

Serum ISM1 levels were determined by an ELISA kit (Biomatik, Delaware, USA), following the manufacturer's protocol. The concentration detection range of human ISM1 was 0.156–10 ng/mL, and intra-assay and inter-assay coefficients of variability (CV) (%) were less than 10% and 12%, respectively. The samples were diluted according to the manual and pre-test.

Measurement of Na^+ in urine and other indicators

Before taking the urine samples, 10 hypertensive patients and 11 healthy age-matched subjects adhered to a diet aimed at 5 g salt (NaCl/24 h) [23] intake for 7 days. To assess nocturnal urinary sodium excretion, sodium concentrations was determined in a sample from a single nocturnal urine collection. Urine samples were stored at − 80 °C. The serum insulin levels were assayed using an ELISA kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The detection range of insulin was 1–300 mIU/L, and intra-assay and inter-assay CVs were less than 10% and 12%, respectively. The concentration of urine Na^+ as measured by a sodium test kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Total nocturnal sodium excretion was taken as the sodium concentration × nocturnal urine volume. The detection ranges of Na^+ were 70–210 mmol/L. The intra-assay CVs were 1.5%, while the inter-assay CVs were less than 5.0%.

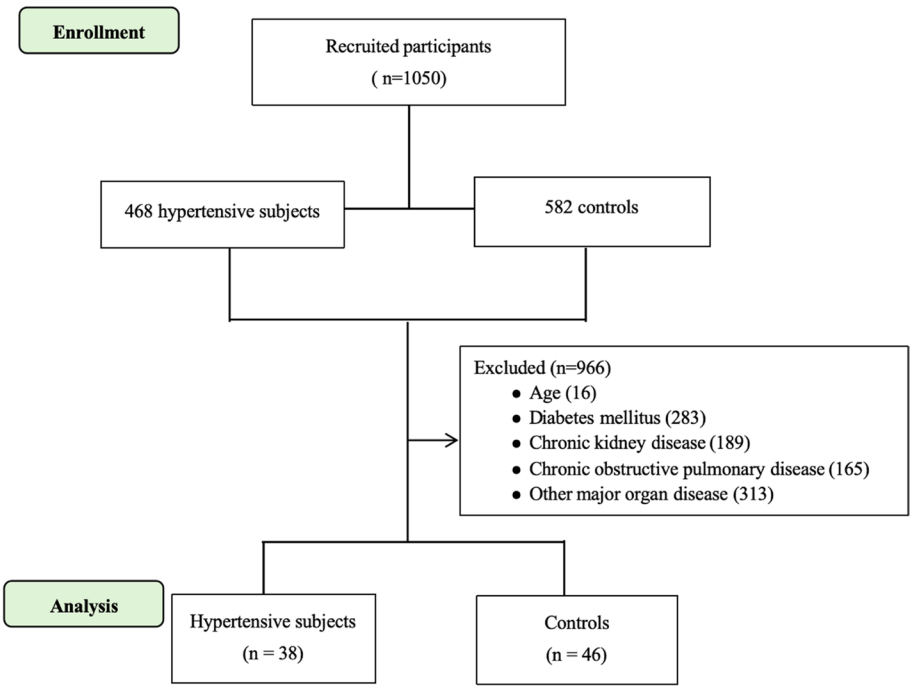

Fig. 1 Flow diagram of participants in the study

Clinical data collection

Blood samples for biochemical determination were obtained in the morning from each subject, after a minimum of 8 h fasting. Serum aliquots were stored frozen at − 80 °C until analysis. The characteristics of all subjects were collected using the computerized patient record system of The Third Affiliated Hospital of Chongqing Medical University. Body mass index (BMI) was calculated as the weight (kg) divided by the squared height (m^2). Triglyceride-glucose index (TyG index) was calculated as = Ln [triglyceride (mg/dl) × glucose (mg/dl)/2] [24]. Insulin resistance was defined by a HOMA-IR index according to the previous studies (≥ 2.54) [25]. Homeostasis Model of Insulin Resistance (HOMA-IR) was calculated as fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [26]. The degree of peripheral arterial arteriosclerosis was estimated by using peripheral arterial hemodynamics BP-203RPE (OMRON, Dalian, China).

Calculation of sample size

There was no report on serum ISM1 in hypertension. T2DM ($n = 17$) and normal glucose-tolerant subjects ($n = 15$) were investigated in a previous study [27]. The Plasma IL-6 levels were 2.1 ± 0.4 pg/mL in the type 2 diabetes mellitus patients and 1.7 ± 0.4 pg/mL in the normal glucose-tolerant group. The ratio of case to control was set at 1.13 (17/15). The power was set at 0.9 and α at 0.05, calculated using PASS software 15.0. Thus, 21 and 24 participants should be recruited in hypertension and healthy individuals, respectively. Considering a 20% loss of study subjects, at least 26 hypertensive participants and 29 healthy controls had to be recruited.

Statistical analysis

All analyses were performed with SPSS version V.26.0 (SPSS, Chicago, USA). Graphs were constructed using the GraphPad Prism software. Data with normal distribution were expressed as mean ± SD, and data that were not normally distributed were expressed as median (interquartile range). Normal distribution of the data was tested by Shapiro–Wilk test. The *t* test was used to compare two independent normally distributed samples. Continuous variables with skewed distribution compared using the Mann–Whitney test. By controlling co-variables, Spearman correlation analysis and partial correlation analysis were used to evaluate the correlation between ISM1 and each variable. Multiple linear regression was used to determine the variables that were independently correlated with ISM1. ROC was used to evaluate the sensitivity of ISM1 in predicting abnormal urine Na^+ excretion and insulin resistance. A value of $P < 0.05$ was considered statistically significant.

Results

Characteristics of subjects

The demographic, anthropometric, and metabolic parameters of 38 hypertensive participants and 46 healthy controls are summarized in Table 1. The control and hypertensive groups had similar distributions in sex, age, heart rate, height, total cholesterol, total bilirubin, urea, creatinine, estimated glomerular filtration rate (eGFR), platelet count, and lymphocyte count. However, HDL-C, nocturnal urine Na^+ concentration, and nocturnal urine Na^+ excretion were higher in the control group, while SBP, DBP, weight, BMI, brachial ankle pulse wave velocity, glucose, triglyceride, low-density lipoprotein cholesterol, TyG index, insulin, and homeostasis model assessment for insulin resistance (HOMA-IR) were significantly higher in the hypertensive group.

Table 1 Clinical features and serum ISM1 levels in healthy- and hypertensive subjects

Feature	Healthy Subjects	Hypertensive Subjects	*P* value
Male/ Female	23/23	24/14	0.227
Age (years)	51.5 (46.75–55)	53.5 (45.25–60.5)	0.336
HR (bpm)	81.33 ± 10.696	82.34 ± 13.107	0.697
Height (cm)	161.076 ± 9.124	164.292 ± 9.030	0.116
Weight (kg)	60.5 (53.65–66.6)	68.65 (62.575–80)	0.000**
BMI (kg/m^2)	23.481 ± 2.578	26.078 ± 2.888	0.000**
SBP (mmHg)	120.5 (113.75–129)	153 (148.75–161.25)	0.000**
DBP (mmHg)	69 (63.75–73.25)	94.5 (84–100)	0.000**
baPWV right (cm/s)	1326 (1234.25–1471.75)	1742 (1514.5–2033)	0.000**
baPWV left (cm/s)	1355 (1234–1488.25)	1699 (1480.5–2059)	0.000**
Glucose (mmol/L)	4.97 (4.538–5.443)	5.195 (4.81–5.678)	0.04*
TG (mmol/L)	1.13 (0.88–1.79)	1.625 (1.225–3.05)	0.001**
TC (mmol/L)	4.98 (4.42–5.533)	5.365 (4.64–5.705)	0.285
HDL-C (mmol/L)	1.34 (1.15–1.55)	1.16 (1.08–1.338)	0.025*
LDL-C (mmol/L)	2.97 (2.575–3.50)	3.385 (2.875–3.81)	0.043*
UA (μmol/L)	331.63 ± 80.613	412.32 ± 88.177	0.000**
ALT (U/L)	20 (14.5–30.25)	30.5 (17.75–51)	0.02*
AST (U/L)	20 (17–26)	25 (20.5–34)	0.007**
Albumin (g/L)	44.350 ± 3.277	46.258 ± 2.505	0.004**
TBil (μmol/L)	12.1 (9.475–17.175)	13.65 (10.425–16.7)	0.297
Urea (mmol/L)	4.939 ± 1.282	5.255 ± 1.012	0.220
Creatinine (μmol/L)	64.04 ± 14.308	68.53 ± 14.821	0.163
eGFR ($ml/min/1.73m^2$)	109.593 ± 20.333	103.347 ± 17.582	0.140
WBC ($10^9/L$)	5.455 (4.348–6.9)	6.385 (5.593–7.043)	0.011*
RBC ($10^{12}/L$)	4.793 ± 0.523	5.050 ± 0.433	0.018*
PLT ($10^9/L$)	222.5 (163.75–249.25)	219 (184.25–244.75)	0.822
Neu ($10^9/L$)	2.925 (2.185–3.938)	3.745 (3.24–4.478)	0.003**
Lym ($10^9/L$)	1.865 (1.58–2.383)	2.115 (1.59–2.543)	0.483
Mon ($10^9/L$)	0.34 (0.25–0.413)	0.405 (0.325–0.43)	0.05*
TyG Index	4.547 (4.427–4.797)	4.796 (4.599–5.186)	0.000**
Insulin (mIU/L)	11.509 (9.748–15.134)	19.442 (15.248–32.605)	0.000**
HOMA-IR	2.665 (2.033–3.297)	4.729 (3.280–7.411)	0.000**
Nocturnal urine Na^+ concentration (mmol/L)	210.791 (194.033–242.009)	139.703 (131.893–146.525)	0.000**
Nocturnal urine Na^+ excretion (mmol/8 h)	76.958 (64.959–97.127)	60.072 (50.119–65.936)	0.004**

Data are expressed as mean ± SD, median (interquartile range)

SBP Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *BMI* Body mass index, *baPWV* Brachial-ankle pulse wave velocity, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *UA* Uric acid, *ALT* Alanine aminotransferase, *AST* Aspartate transaminase, *TBil* Total bilirubin, *WBC* White blood count, *RBC* Red blood count, *PLT* Platelet, *Neu* Neutrophil count, *Lym* Lymphocyte count, *Mon* Monocyte count, *TyG* Index, triglyceride-glucose index, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *ISM1* isthmin-1. *$P < 0.05$, **$P < 0.01$ vs. controls

Circulating concentrations of ISM1 and blood pressure

Elevated serum ISM1 levels were observed in hypertensive participants compared to healthy volunteers (Fig. 2). Furthermore, we noticed that ISM1 serum levels were positively correlated with SBP ($r_s = 0.748$, $P < 0.01$) and DBP ($r_s = 0.568$, $P < 0.01$), even age, BMI, sex, heart rate, glucose, total cholesterol and eGFR were adjusted (Table 2).

Circulating ISM1 and clinical characteristics

We conducted Spearman correlation analysis to assess the relationships between ISM1 and various parameters listed in Table 2. Our findings demonstrated positive correlations between circulating ISM1 levels and BMI, glucose, uric acid, albumin, insulin, HOMA-IR, TyG index, triglyceride and red blood count. Significant positive correlations were also observed between serum ISM1 levels and both SBP and DBP (Fig. 3A and B). Since sodium homeostasis plays a crucial role in long-term blood pressure regulation [28], we explored the association between ISM1 serum levels and nocturnal urine Na^+ concentration and excretion, revealing a negative correlation (Fig. 3C and D). Furthermore, our investigation revealed a positive correlation between ISM1 levels and brachial-ankle pulse wave velocity (baPWV) (Fig. 3E and F), an indicator of arterial stiffness and endothelial dysfunction, implicating its involvement in blood pressure regulation.

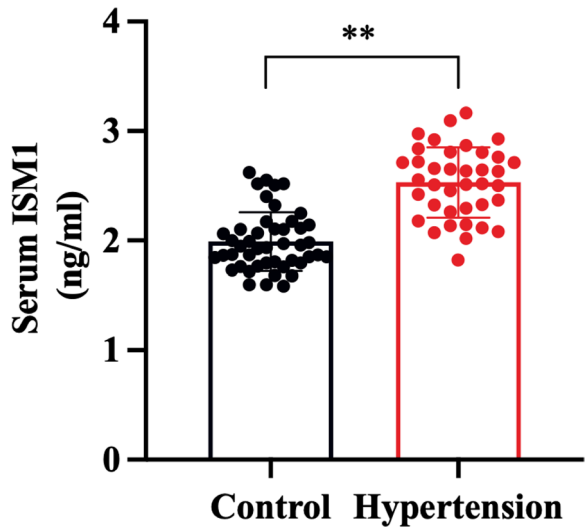

Fig. 2 The levels of circulating ISM1 in healthy subjects (control) and subjects with newly-diagnosed essential hypertension (**$P < 0.001$ vs. control)

Clinical parameters independently associated with circulating ISM1

During univariate analysis, confounding factors were not considered, potentially impacting the correlation between ISM1 and other variables. Specifically, multiple linear regression analysis revealed that SBP was independently associated with circulating serum ISM1 levels. The multiple regression equation derived from this association is as follows: $Y_{ISM1} = -2.811 + 0.037X_{SBP}$ ($R^2 = 0.971$).

Prediction of serum ISM1 in abnormal Na^+ excretion and insulin resistance

Previous study had shown that sodium excretion was associated with increased risk of hypertension among adults in China [29]. Our study had revealed that there was a negative correlation between ISM1 levels and nocturnal urine Na^+ excretion. Furthermore, nocturnal renal Na^+ excretion was divided into high and low excretion groups according to media. The AUROC of circulating ISM1 level to predict low renal Na^+ excretion was 0.873 (Fig. 4). In addition, we also used circulating ISM1 level to predict HOMA-IR, which showed that the AUROC was 0.740 (Fig. 5).

Discussion

In this study, we observed higher serum levels of the adipokine ISM1 in individuals with essential hypertension compared to control subjects. Moreover, ISM1 exhibited an inverse correlation with both nocturnal urine Na^+ concentration and nocturnal urine Na^+ excretion. These findings suggest that ISM1 may serve as a novel biomarker for abnormal urine Na^+ excretion.

To our knowledge, this study represents the first investigation into the relationship between serum ISM1 levels and essential hypertension in a population-based cohort. Our results revealed elevated ISM1 levels in hypertensive individuals compared to healthy volunteers, with a strong positive association between serum ISM1 levels and both SBP and DBP, even after adjusting for age, BMI, sex, heart rate, glucose, total cholesterol, and eGFR. Previous prospective studies have highlighted the association between various adipokines and essential hypertension. For instance, adiponectin has demonstrated beneficial effects of antihypertensive properties [7]. Chemerin levels are positively correlated with high glucose and LDL levels [8]. Vaspin treatment has shown to prevent systolic blood pressure elevation in spontaneously hypertensive rats [10]. Additionally, a positive association has been observed between plasma leptin and incident hypertension in large prospective cohorts of Black individuals

Table 2 Correlations analysis between serum ISM1 and clinical parameters

Feature	Circulating ISM1			
	r_s	*P* value	Adjusted r_s [a]	*P* value
Sex	-0.108	0.327		
Age (years)	0.097	0.378		
SBP (mmHg)	0.923	0.000	0.748	0.000
DBP (mmHg)	0.724	0.000	0.568	0.000
HR (bpm)	0.119	0.281		
Height (cm)	0.114	0.307		
Weight (kg)	0.382	0.000		
BMI (kg/m^2)	0.464	0.000		
baPWV right (cm/s)	0.611	0.000	0.344	0.012
baPWV left (cm/s)	0.653	0.000	0.350	0.011
Glucose (mmol/L)	0.272	0.012		
TG (mmol/L)	0.374	0.000	0.133	0.274
TC (mmol/L)	0.137	0.213		
HDL-C (mmol/L)	-0.271	0.016	0.005	0.970
LDL-C (mmol/L)	0.200	0.077	0.031	0.801
UA (μmol/L)	0.386	0.000	0.127	0.296
ALT (U/L)	0.186	0.090	-0.078	0.521
AST (U/L)	0.144	0.193	-0.129	0.287
Albumin (g/L)	0.270	0.013	0.267	0.026
TBil (μmol/L)	0.138	0.210	-0.045	0.710
Urea (mmol/L)	0.048	0.664	-0.079	0.513
Creatinine (μmol/L)	0.099	0.373	0.002	0.987
eGFR ($ml/min/1.73m^2$)	-0.081	0.465		
WBC ($10^9/L$)	0.08	0.472	-0.019	0.873
RBC ($10^{12}/L$)	0.255	0.019	0.178	0.141
PLT ($10^9/L$)	0.004	0.970	0.090	0.458
Neu ($10^9/L$)	0.150	0.172	0.017	0.886
Lym ($10^9/L$)	-0.092	0.403	-0.114	0.346
Mon ($10^9/L$)	0.066	0.549	-0.120	0.323
TyG Index	0.403	0.000	0.129	0.287
Insulin (mIU/L)	0.547	0.000	0.296	0.012
HOMA-IR	0.548	0.000	0.286	0.015
Nocturnal urine Na^+ concentration (mmol/L)	-0.753	0.000	-0.710	0.010
Nocturnal urine Na^+ excretion (mmol/8 h)	-0.674	0.001	-0.609	0.036

Abbreviations: *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *BMI* Body mass index, *baPWV* Brachial-ankle pulse wave velocity, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *UA* Uric acid, *ALT* Alanine aminotransferase, *AST* Aspartate transaminase, *TBil* Total bilirubin, *WBC* White blood count, *RBC* Red blood count, *PLT* Platelet, *Neu* Neutrophil count, *Lym* Lymphocyte count, *Mon* Monocyte count, *TyG Index* Triglyceride-glucose index, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *ISM1* Isthmin-1

[a] adjusted for age, BMI, sex,HR,glucose, TC, eGFR

[11]. These findings indicated the significant role of adipokines in the essential hypertension.

Biologically, the positive association between ISM1 and blood pressure progression is plausible. Recent studies have indicated that ISM1 inhibits nuclear factor kappa-B (NF-κB) activation and proinflammatory cytokines production [30], thereby exerting anti-inflammatory effects. ISM1, as an anti-inflammatory protein, selectively triggers the apoptosis of alveolar macrophages and protects lung homeostasis [31]. Previous study indicated that blockade of NF-κB reduces renal angiotensin II type 1 receptor (AT_1R) expression and function, improves inflammatory/anti-inflammatory balance, which lowers blood pressure and recovers renal function [32]. Therefore, ISM1 may play a protective role in high blood pressure through restraining renal inflammation.

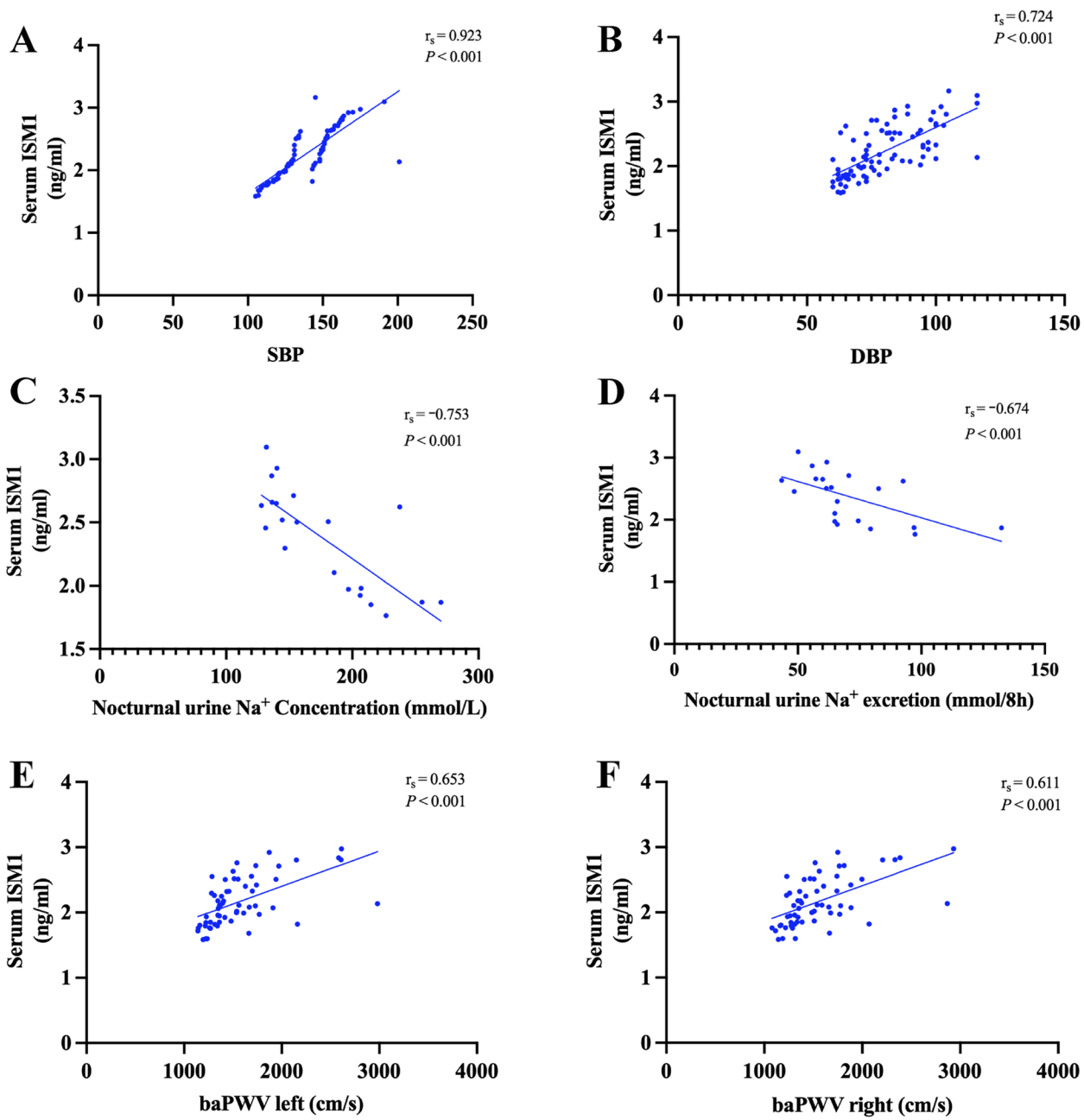

Fig. 3 Association of circulating ISM1 levels and clinical parameters, including **A** SBP, **B** DBP, **C** nocturnal urine Na^+ concentration, **D** nocturnal urine Na^+ excretion, **E** baPWV left, **F** baPWV right. SBP, systolic blood pressure; DBP, diastolic blood pressure; baPWV, brachial-ankle pulse wave velocity

The kidneys play an important role in the long-term regulation of blood pressure [33]. Urinary sodium excretion was closely related to blood pressure, every 100 mmol/d reduction in urinary sodium excretion was associated with a lower mean SBP of 5.56 mmHg (95% CI, − 4.52 to − 6.59) and a lower mean DBP of 2.33 mmHg (95% CI, − 1.66 to − 3.00) [34]. In the present study, we found that circulating ISM1 levels were negative associated with nocturnal urine Na^+ concentration and nocturnal urine Na^+ excretion. Study in patients with type 2 diabetes mellitus (T2DM) found that serum ISM1 levels were increased in patients with decreased eGFR [35]. Serum ISM1 levels were positively and independently correlated with the severity of albuminuria in patients with T2DM [36], suggesting that ISM1 may be associated with renal dysfunction. Our results showed

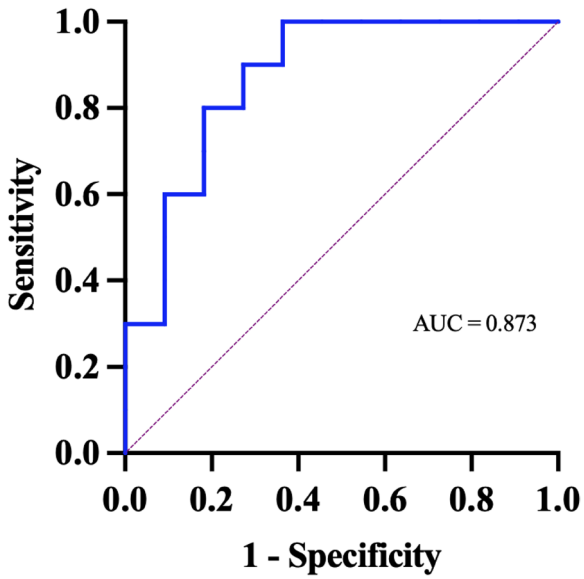

Fig. 4 The AUROC of circulating ISM1 levels to predict low renal Na^+ excretion

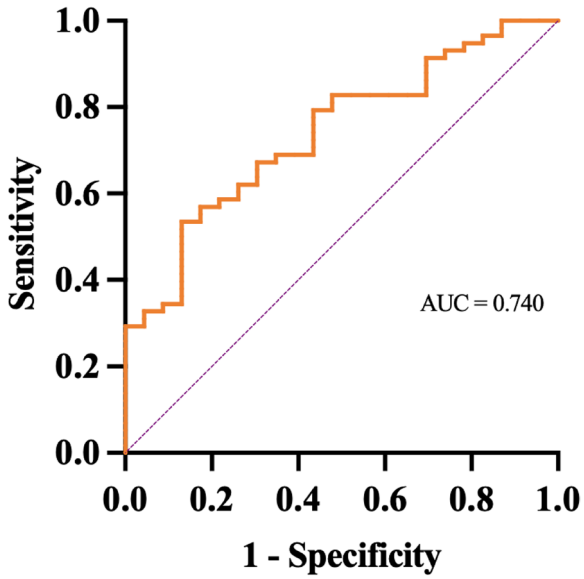

Fig. 5 The AUROC of circulating ISM1 levels to predict HOMA-IR

that serum ISM1 levels may potentially serve as predictors of abnormal urine Na^+ excretion in hypertensive individuals.

On the other hand, five indices for insulin resistance were assessed in clinical practice [37]. We found that serum ISM1 levels can be used to predict HOMA-IR in the current study. However, it should be noted that HOMA-IR is not the gold standard for diagnosing insulin resistance though it is non-invasive and widely used in clinical and research settings. Alternative methods, including the hyperinsulinemic-euglycemic clamp [38], would be needed to verify the relationship between ISM1 and insulin resistance in the future. Once the underlying causal relationship is better elucidated, ISM1 is expected to be used for preliminary clinical screening for insulin resistance.

In this study, we observed that the positive relation between ISM1 levels and baPWV. Study have indicated that the blood pressure variability is an independent predictor of unfavorable baPWV levels and precedes arteriosclerosis progression, especially in people with hypertension [39], which raised the possibility that baPWV may link ISM1 with essential hypertension. Nevertheless, it should be noted that baPWV had not been found to be a variable that was independently correlated with circulating ISM1 levels.

In summary, our results demonstrated that the serum ISM1 levels were increased in patients with essential hypertension, and ISM1 levels were positively associated with both SBP and DBP. Especially, ISM1 may represent a promising novel predictor for abnormal Na^+ excretion and insulin resistance, which could provide support for individualized, precision medication management, and earlier lifestyle interventions for management on hypertensive patients. Further longitudinal studies and basic experiments are warranted to validate these findings.

Limitations

Our study has several limitations. First, it was a case–control study without follow-up assessments, which limited our ability to establish causal relationships. Second, the sample size was relatively limited. Furthermore, all participants were of Chinese ethnicity, raising questions about the generalizability of our findings to other populations. Therefore, larger prospective cohort studies involving more diverse populations are needed in the future.

Conclusion

Serum ISM1 levels were increased in patients with essential hypertension, ISM1 levels were positively associated with SBP and DBP. ISM1 may potentially serve as a potential biomarker of abnormal urine Na^+ excretion and insulin resistance in primary hypertensive individuals.

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Not applicable.

Authors' contributions
D.C.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. Z.X.: Methodology, Project administration, Resources, Software, Funding acquisition, Writing – review &editing. Z.L.: Investigation, Data curation, Methodology. Y.Q.: Investigation, Methodology, Software. L.C.: Investigation, Methodology, Software. Z.Y.: Project administration, Supervision, Resources, Validation. Y.J.: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. All authors reviewed the manuscript.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All protocols in this study were followed conducted in accordance with the Helsinki Declaration (1989 revision). The ethics committee of The Third Affiliated Hospital of Chongqing Medical University provided the approval of this study. All experimental protocols were approved by the institutional ethical board, all methods were carried out in accordance with relevant guidelines and regulations, and written informed consents were obtained from all subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Nicholas W S Chew, Cheng Han Ng, Darren Jun Hao Tan, et al. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metab. 2023;35(3):414–428.e3.
2. Bin Zhou, Rodrigo M Carrillo-Larco, Goodarz Danaei, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957–980.
3. Wang J-G, Zhang W, Li Y, et al. Hypertension in China:epidemiology and treatment initiatives. Nat Rev Cardiol. 2023;20(8):531–45.
4. Global report on hypertension: the race against a silent killer. Geneva: World Health Organization. 2023. Licence: CC BY-NC-SA 3.0 IGO.
5. Quesada O, Claggett B, Rodriguez F, et al. Associations of insulin resistance with systolic and diastolic blood pressure: a study from the HCHS/SOL. Hypertension. 2021;78(3):716–25.
6. Niu Z, Qingqing Wu, Luo Y, et al. Plasma lipidomic subclasses and risk of hypertension in middle-aged and elderly Chinese. Phenomics. 2022;2(5):283–94.
7. Han W, Yang S, Xiao H, et al. Role of adiponectin in cardiovascular diseases related to glucose and lipid metabolism disorders. Int J Mol Sci. 2022;23(24):15627.
8. Jaspreet Kaur, Harman S. Mattu, Kamaljit Chatha,Harpal S Randeva. Chemerin in human cardiovascular disease. Vascul Pharmacol. 2018;110:1–6.
9. Lunbo Tan, Xifeng Lu, A.H.Jan Danser, et al. The Role of Chemerin in Metabolic and Cardiovascular Disease: A Literature Review of Its Physiology and Pathology from a Nutritional Perspective. Nutrients. 2023;15(13):2878.
10. Kameshima S, Sakamoto Y, Okada M, et al. Vaspin prevents elevation of blood pressure through inhibition of peripheral vascular remodelling in spontaneously hypertensive rats. Acta Physiol. 2016;217(2):120–9.
11. Arnaud D Kaze, Solomon K Musani, Aurelian Bidulescu, et al. Plasma Leptin and Blood Pressure Progression in Blacks: The Jackson Heart Study. Hypertension. 2021;77(4):1069–1075.
12. Pera EM, Kim JI, Martinez SL, et al. Isthmin is a novel secreted protein expressed as part of the Fgf-8 synexpression group in the Xenopus midbrain–hindbrain organizer. Mech Dev. 2002;116(1–2):169–72.
13. Min Hu, Zhang X, Can Hu, et al. A brief overview about the adipokine: Isthmin-1. Front Cardiovasc Med. 2022;9:939757.
14. Jiang Z, Zhao M, Voilquin L, et al. Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. Cell Metab. 2021;33(9):1836-1852.e11.
15. Senturk Z, Kalea I, Muhcu M. Investigation of serum isthmin 1 concentration in pregnant women diagnosed with gestational diabetes mellitus; a case-control study. J Matern Fetal Neonatal Med. 2023;36(2):2271624.
16. Francisco Javier Ruiz-Ojeda, Augusto Anguita-Ruiz, Maria C. Rico, et al. Serum levels of the novel adipokine isthmin-1 are associated with obesity in pubertal boys. World Journal of Pediatrics. 2023;19(9):864–872.
17. Nithya RAO, Yu Fei Lee, Ruowen GE. Novel endogenous angiogenesis inhibitors and their therapeutic potential, Acta Pharmacologica Sinica. 2015;36(10):1177–90
18. Feng RQ, Xu MY, Feng RY, Zhang L, Yin XF, Wang C, Liu JB. Serum Isthmin-1 is negatively correlated with HDL-C in type 2 diabetes mellitus. J Diabetes Complications. 2023;37(10):108567.
19. Wang C, Xu M, Feng R, Zhang L, Yin X, Feng R, Liang K, Liu J. Serum isthmin-1 levels are positively and independently correlated with albuminuria in patients with type 2 diabetes mellitus. BMJ Open Diabetes Res Care. 2022;10(5):e002972.
20. Lei X, Chen H, Xu Y, Yang Z, Zhang L, Wang C, Du H. Serum isthmin-1 is a potential biomarker for metabolic dysfunction associated fatty liver disease in patients with metabolic syndrome and type 2 diabetes mellitus. BMJ Open Diabetes Res Care. 2024;12(5):e004514.
21. Nicholas W S Chew, Cheng Han Ng, Darren Jun Hao Tan, et al. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metab. 2023;35(3):414–428.
22. Joint Committee for Guideline Revision. 2018 Chinese guidelines for prevention and treatment of hypertension-A report of the revision committee of Chinese guidelines for prevention and treatment of hypertension. J Geriatr Cardiol. 2019;16(3):182–241.
23. O'Donnell M, Mente A, Alderman MH, et al. Salt and cardiovascular disease: insufficient evidence to recommend low sodium intake. Eur Heart J. 2020;41(35):3363–73.
24. Alizargar J, Bai C-H, Hsieh N-C, et al. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. Cardiovasc Diabetol. 2020;19(1):8.
25. Lin D, Qi Y, Huang C, et al. Associations of lipid parameters with insulin resistance and diabetes: A population-based study. Clin Nutr. 2018;37(4):1423–9.
26. Dicky Levenus Tahapary, Livy Bonita Pratisthita, Nissha Audina Fitri, et al. Challenges in the diagnosis of insulin resistance: focusing on the role of HOMA-IR and Tryglyceride/glucose index, Diabetes Metab Syndr. 2022;16(8):102581
27. G. Daniele, R. Guardado Mendoza, D. Winnier. et al.The inflammatory status score including IL-6, TNF-a, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetol. 2014; 51:123–131.
28. Brands MW. Role of insulin-mediated antinatriuresis in sodium homeostasis and hypertension. Hypertension. 2018;72(6):1255–62.
29. Li Y, Zhang P, Jing Wu, et al. Twenty-four-hour urinary sodium and potassium excretion and their associations with blood pressure among adults in china: baseline survey of action on salt China. Hypertension. 2020;76(5):1580–8.
30. Nguyen N, Simin Xu, Lam TYW, et al. ISM1 suppresses LPS-induced acute lung injury and post-injury lung fbrosis in mice. Mol Med. 2022;28(1):72.
31. Terence Y W Lam, Ngan Nguyen, Hong Yong Peh, et al. ISM1 protects lung homeostasis via cell-surface GRP78-mediated alveolar macrophage apoptosis. Proc Natl Acad Sci USA. 2022;119(4):e2019161119.

32. Luo H, Wang X, Wang J, et al. Chronic NF-κB blockade improves renal angiotensin II type 1 receptor functions and reduces blood pressure in Zucker diabetic rats. Cardiovasc Diabetol. 2015;10(14):76.
33. Tian Z, Liang M. Renal metabolism and hypertension. Nat Commun. 2021;12(1):963.
34. Tommaso Filippini, Marcella Malavolti, Paul K Whelton, et al. Blood Pressure Effects of Sodium Reduction: Dose-Response Meta-Analysis of Experimental Studies. Circulation. 2021;143(16):1542–1567.
35. Mingyue Xu, Feng R, Feng R, et al. Glomerular filtration rate in patients with type 2 diabetes mellitus: is serum isthmin-1 level a possible link? BMJ Open Diab Res Care. 2023;11(4):e003402.
36. Wang C, Mingyue Xu, Feng R, et al. Serum isthmin-1 levels are positively and independently correlated with albuminuria in patients with type 2 diabetes mellitus. BMJ Open Diab Res Care. 2022;10(5):e002972.
37. Justin B Echouffo-Tcheugui, Sui Zhang, John W McEvoy, et al. Insulin Resistance and N-Terminal Pro-B-Type Natriuretic Peptide Among Healthy Adults. JAMA Cardiol. 2023;8(10):989–995.
38. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. Science. 2021;372(6547):1224–9.
39. Zhiyuan Wu, Zhang H, Wang Y, et al. Temporal and Bidirectional Association Between Blood Pressure Variability and Arterial Stiffness: Cross-Lagged Cohort Study. JMIR Public Health Surveill. 2023;9:e45324.

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