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Association of Serum Uric Acid with Indices of Insulin Resistance: Proposal of a New Model with Reference to Gender Differences

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Background: Insulin resistance (IR) is a key feature of type 2 diabetes (T2D) and an independent risk factor for metabolic syndrome. Previous studies have linked elevated serum uric acid (SUA) to an increased risk of T2D.

Aim: The purpose of this study was to investigate the relationship between SUA and IR. At the same time, the correlation between New model and SUA compared with other IR alternatives was compared, so as to provide a simple and effective new indicator for early detection and prediction of IR risk and early prevention of T2D.

Methods: The first cohort was the Discovery Cohort, which included 318 obese patients. And the second cohort was the Verification Cohort, which included a total of 4333 subjects who underwent a routine health checkup at our hospital. Spearman correlation analysis and binary logistic regression analysis were used to discuss the correlation between SUA and IR.

Results: Regardless of sex, fasting insulin (FINS) and IR replacement markers increased with SUA ($P<0.001$). In both cohorts, SUA was associated with IR alternatives, especially with New model, and differed between men and women in all correlation analyses. After adjusting for confounding factors, SUA was still associated with IR ($P<0.001$).

Conclusion: The correlation between SUA and IR was significantly stronger in women than in men. And the correlation between SUA and New model is stronger than other IR replacement models. However, the causal relationship between SUA and IR has not been clearly established.

Keywords: insulin resistance, serum uric acid, HDL-c, triglycerides

Introduction

There are approximately 537 million cases of diabetes worldwide, of which type 2 diabetes (T2D) accounts for nearly 90%, and the prevalence is still increasing.[1] The prevalence of T2D is increasing, and the age of onset is becoming younger and younger. In the early stages of T2D, insulin concentration is elevated to try to decrease glucose, but the body is "resistant" to this elevated blood insulin.[2] This process is described as insulin resistance (IR). The heart relies on insulin signaling to manage myocardial matrix supply and directly affect myocardial metabolism, and IR disrupts this process, leading to severe myocardial disorders and increasing the risk of coronary artery disease and heart failure.[3] IR is associated with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD).[4] IR-induced reduced inhibition of lipolysis at the adipose tissue level and increased production of new liver fat, gradually evolving into cirrhosis, and T2D has been identified as an independent risk factor for the development of non-viral hepatocellular carcinoma (HCC).[5] IR can also worsen our memory and gradually become a potential feature of Alzheimer's disease.[6] Therefore, the early prevention and treatment of T2D is essential.

Although many risk factors for diabetes have been recognized, such as obesity, advanced age, and high blood pressure. Even after the traditional control of blood sugar and obesity, which are two important risk factors, the incidence of diabetes and macrovascular complications is increasing year by year. What's more, early studies have

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shown that IR is related to hyperuricemia,[7] which also provides a new perspective for us to control IR. More and more studies focus on SUA. Previous data[8] showed that approximately 17.4% of individuals in China suffered from hyperuricemia. Hyperuricemia is associated with numerous long-term health conditions. A prospective study in Taiwan suggested that uric acid extended the association with the future risk of T2D.[9] However, the direct relationship between SUA and the development of T2D remains controversial.

At present,[10] the hyperinsulin normal glucose clamp technique (HEC) is considered to be the most accurate method for assessing IR, but the operation is complicated, expensive and invasive, so it is not suitable for the promotion of large sample populations. HOMA-IR is considered as an alternative indicator of this technique, but the measurement is not accurate enough and the repeatability is poor. In addition to HOMA-IR, Adipose tissue insulin resistance (ADIPO-IR), TyG and TG/HDL-c can also be used to represent IR. In the early stage, our team first screened the risk factors of IR through univariate logistic regression analysis. Multivariate logistic regression analysis was performed, and four variables, namely visceral fat area (VFA), triacylglycerol (TG), fasting blood glucose (FPG) and alanine aminotransferase (ALT), were identified as risk factors for IR. We then used VFA, age, ALT, TG, FPG to construct a new model that is convenient for clinical application based on an easily accessible and low-cost prediction model of IR measurement parameters, and shows high predictive power.[11]

Hence, we aimed to explore the correlation between SUA and IR by using the multiple IR substitutes represented by New model and to facilitate early detection of IR in patients with hyperuricemia.

Methods

Subjects

Study population is made up of two cohort. The first cohort, the discovery cohort, consisted of 439 subjects, of which 115 subjects underwent a health check between September 2021 and January 2022 and the other 324 subjects were patients who attended an obesity clinic between January 2021 and June 2022. Participants with no recorded laboratory results, participants under 18 years of age, individuals who may affect uric acid levels (such as purine metabolism disorders, renal failure, polycystic kidney disease, urinary stones, and participants taking medications that affect plasma uric acid levels), and individuals who had taken hypoglycemic medications were excluded from the study. A total of 110 patients were excluded. The second cohort was the Verification Cohort, which selected 4333 subjects who underwent physical examination at the Health Management Center of Tianjin People's Hospital from August to November 2020. People under the age of 18, pregnant women, people with incomplete basic information, people with a pacemaker implant and people with mental illness have been excluded. A total of 35 patients were excluded. The Ethics Committee of Tianjin People's Hospital has reviewed and approved this study (No. 2021C06). The study complies with the Declaration of Helsinki. All subjects signed informed consent forms.

Clinical Measurement and Assessment of Body Composition

Basic characteristics (including age, sex, height, and weight) were recorded. Weight and height were evaluated by the DST-600 fully automatic height and weight instrument with 0.1 kg of accuracy. Body mass index (BMI) was obtained by dividing weight (kg) by the square of height (m2). Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured by a fully automated electronic sphygmomanometer, which was measured twice for each subject in a quiet state. Body composition was assessed by the bioelectrical impedance analysis method (Inbody770, Bio-space Inc., Korea), which is a very reliable and popular tool to assess body fat distribution and the distribution of individual components. All subjects were asked to wear light clothing, remove shoes and socks, remove metal accessories, and then stand upright on the electrode. The test measures skeletal muscle mass (SMM), fat-free mass (FFM), visceral fat area (VFA), and body fat percentage (PBF).

Laboratory Measurements

Venous blood samples were collected from all participants, centrifuged to obtain serum samples, and stored in a refrigerator at − 80 degrees until thawed when the samples needed to be analyzed. The levels of free fatty acids

(FFAs), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and serum uric acid (SUA) were determined analyzed using an automated biochemical analyzer (TBA120FR, Toshiba, Japan). According to the Chinese guidelines for preventing and treating hyperuricemia, hyperuricemia is defined as adult fasting blood uric acid greater than or equal to 420 μmol/L, no longer distinguishing between males and females. Fasting insulin (FINS) was detected by chemiluminescence immunoassay.

Calculation and Definition of IR

Homeostatic model assessment of IR (HOMA-IR)[12] was calculated as fasting insulin (FINS, μU/mL) × fasting plasma glucose (FPG, mmol/L)/22.5. At present, the Chinese epidemiological surveys[13] have defined IR with a HOMA-IR value of 2.69 in adults. Adipo-IR[14] was calculated as FINS (μ U/mL) ×free fatty acid (FFA) (mmol/L). TyG index[15] is calculated by using the equation Ln [FPG (mg/dL) x TG (mg/dL)/2]. The TG/HDL-C ratio was calculated as TG (mg/dL) divided by HDL-C (mg/dL). Since visceral obesity plays a significant role in the development of insulin resistance (IR),[16] our team has done extensive preliminary work and proposed a new IR prediction model (New Model)[11] whose calculation formula includes visceral obesity indicators. The prediction value of New model for IR has been confirmed by comparing it with other IR substitutes. The formula of the predictive model was (1.4892 × Ln VFA + 0.6906 × Ln ALT +0.4966 × Ln TG + 2.784 × Ln FPG +0.0293 × age)/2, and the cut-off value of New model is calculated to be 8.18.

Statistical Analysis

The extreme values and missing values were processed and all data were imported into SPSS 27.0 statistical software for data analysis. The Shapiro–Wilk test was used to check whether the data distribution was normal. The mean ± standard deviation (SD) was used if the data was normally distributed, and the median (interquartile) was used if the data were not normally distributed. Analysis of variance between groups was performed using the one-way ANOVA or unpaired *T*-test for continuous variables that obeyed a normal distribution. The pairwise comparison was performed by TukeyHSD test. And the Mann–Whitney *U*-test for continuous variables that did not obey a normal distribution or obeyed a normal distribution with uneven variance. Post-hoc pairwise comparisons were performed using the Bonfferroni test. To investigate the relationship between SUA and IR, Spearman correlation analysis was performed. The confounding factors were adjusted by linear regression. To evaluate the prevalence risk of IR, binary logistic regression analysis was adopted to estimate the odds ratio (OR) and 95% confidence interval (CI) between SUA and IR. All statistical tests were statistically significant with $p< 0.05$.

Results

Basic Characteristics of the Two Study Cohorts

Due to sex differences in hyperuricemia incidence and SUA levels, all participants in the discovery cohort were divided into two groups by sex, with each group further classifying enrolled participants into low and high SUA based on diagnostic criteria for hyperuricemia. There were 129 (40.57%) males and 189 (59.43%) females in the study group, including 46 (35.66%) males and 30 (15.87%) females in the HUA group. Table 1 shows the anthropometric characteristics, basic characteristics and metabolic characteristics of the participants in the four groups. Regardless of sex Weight, BMI, Cr, ALT, AST, TG, FINS, VFA, PBF, FMM, SMM, HOMA-IR, Adipo-IR, TyG, TG/HDL-c and New model were significantly higher in the HUA group ($p<0.001$). The median value of SUA was 496.50μmol/L in the male HUA group and 331.00μmol/L in the NUA group. The median value of uric acid was 486.00μmol/L in the female HUA group and 288.00μmol/L in the NUA group. In addition, in males, HbA1c and TC were higher in the HUA group ($p<0.05$), and in females, HDL-c was lower in the NUA group than in the HUA group ($p<0.001$).In all clinical measures, males had significantly higher SUA than females, and the female group had a higher VFA, PBF, FINS, and IR.

The basic clinical characteristics of 4333 subjects in the Verification Cohort were shown in Table 2. The age, SUA, ALT, TG, VFA, PBF, FMM, SMM, TyG, TG/HDL-c and New mode of male group were significantly higher than that of female group ($p<0.001$).

Table 1 Clinical Characteristics of the Discovery Cohort According to Gender and SUA

Items	Male		p	Female		p
	HUA	NUA		HUA	NUA	
N(%)	N=46(35.66%)	N=83(64.34%)		N=30(15.87%)	N=159(84.13%)	
Age(years)	36.26±10.76	37.78±11.48	0.466	35.43±11.36	33.97±9.63	0.346
Height(cm)	175.66±6.58	173.65±6.38	0.092	162.95±5.46	163.26±5.82	0.829
Weight(kg)	101.79±18.54	85.171±21.93	<0.001	93.51±12.88	75.64±20.54	<0.001
BMI(kg/m2)	33.01±5.83	28.35±6.89	<0.001	35.23±4.70	28.43±7.57	<0.001
SBP(mmHg)	135.34±13.60	129.64±17.11	0.054	138.48±24.43	124.60±17.17	<0.001
DBP(mmHg)	83.85±12.52	78.54±11.44	0.016	82.76±13.67	76.02±12.14	0.010
Cr(umol/L)	75.00(67.75,84.00)	71.00(63.75,84.00)	0.254	64.00(57.15,70.62)	57.00(51.68,66.55)	0.009
SUA(μmol/L)	496.50(462.00,558.25)	331.00(288.00,364.00)	<0.001	486.00(449.00,558.00)	288.00(240.00,350.00)	<0.001
AST(U/L)	27.50(22.70,38.35)	21.00(18.00,25.10)	<0.001	31.80(18.55,57.30)	18.70(15.00,30.00)	<0.001
ALT(U/L)	46.95(33.43,66.25)	24.00(16.00,38.60)	<0.001	35.90(20.80,68.60)	18.40(12.9,30.00)	<0.001
FPG(mmol/L)	5.05(4.80,5.39)	4.86(4.50,5.30)	0.178	5.15(4.60,6.27)	4.84(4.45,5.23)	0.013
HbA1c(%)	5.65(5.40,6.00)	5.40(5.30,5.80)	0.151	5.80(5.30,6.05)	5.50(5.30,5.80)	0.008
FFA(mmol/L)	0.89(0.70,1.04)	0.80(0.59,0.98)	0.046	0.80(0.70,1.04)	0.83(0.63,1.06)	0.833
TG(mmol/L)	1.88(1.21,3.27)	1.26(0.92,1.83)	<0.001	2.45(1.22,3.34)	1.19(0.79,1.71)	<0.001
TC(mmol/L)	5.02(4.44,5.86)	4.47(4.11,5.09)	0.004	5.23(4.68,6.30)	4.68(4.12,5.30)	0.001
HDL-c(mmol/L)	1.22(1.02,1.39)	1.29(1.13,1.50)	0.075	1.04(0.89,1.29)	1.46(1.23,1.75)	<0.001
LDL-c(mmol/L)	3.16±0.84	2.90±0.75	0.075	3.63±1.18	2.84±0.72	0.002
VFA(cm2)	167.55±59.41	120.36±69.2	<0.001	209.89±33.20	144.66±66.78	<0.001
PBF(%)	35.98±7.34	29.50±9.82	<0.001	46.14±4.02	38.16±9.21	<0.001
FFM(kg)	63.95±8.10	58.00±8.19	<0.001	49.66±5.63	45.24±7.10	<0.001
SMM(kg)	35.88±4.94	32.54±5.05	<0.001	27.40±3.36	24.68±4.28	<0.001
FINS(μU/mL)	16.70(13.04,26.17)	12.12(7.12,16.55)	<0.001	20.63(16.16,28.83)	14.30(8.19,19.56)	<0.001
TyG	1.63±0.74	1.18±0.55	<0.001	1.76±0.82	1.12±0.69	<0.001
HOMA-IR	3.70(2.77,6.57)	2.51(1.59,3.95)	<0.001	5.53(3.51,8.12)	3.05(1.77,4.52)	<0.001
Adipo-IR	15.38(10.28,28.83)	8.77(4.71,15.31)	<0.001	18.78(11.21,28.17)	11.63(5.21,19.78)	<0.001
TG/HDL-c	1.51(1.01,2.51)	0.94(0.63,1.58)	<0.001	1.97(0.86,3.75)	0.82(0.47,1.31)	<0.001
New model	8.09±0.58	7.44±0.80	<0.001	8.32±0.70	7.40±0.77	<0.001

Note: Continuous data were presented as mean ± standard deviation or median (interquartile range).

Abbreviations: HUA, hyperuricemia; NUA, not hyperuricemia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; SUA, serum uric acid; AST, aspartate transaminase; ALT, alanine transaminase; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FFA, free fatty acids; TG, triglycerides; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; VFA, visceral fat area; PBF, percent body fat; FFM, fat-free mass; SMM, skeletal muscle mass; FINS, fasting insulin; TyG, triglyceride-glucose index; HOMA-IR, homeostatic model assessment of insulin resistance; Adipo-IR, adipose tissue insulin resistance; TG/HDL-c, triglycerides divided by high-density lipoprotein cholesterol; New model, new insulin resistance prediction model.

Table 2 Clinical Characteristics of the Verification Cohort According to Gender

Items	Male	Female	p
N(%)	1812(41.8%)	2521(58.2%)	
Age(years)	45.20±17.80	42.35±13.89	<0.001
Height(cm)	172.42±6.30	160.63±5.58	<0.001
Weight(kg)	76.39±11.37	59.17±8.72	<0.001
BMI(kg/m2)	25.63±3.29	22.94±3.27	0.853
SBP(mmHg)	127.46±16.38	117.83±17.35	0.097
DBP(mmHg)	80.50±10.61	75.02±9.87	0.029
Cr(umol/L)	76.00(69.00,82.00)	56.00(51.00,61.00)	<0.001
SUA(μmol/L)	358.00(317.00,400.00)	268.00(237.00,308.00)	<0.001

(*Continued*)

Table 2 (Continued).

Items	Male	Female	p
ALT(U/L)	22.20(15.70,33.20)	13.00(9.60,18.70)	<0.001
FPG(mmol/L)	5.23(4.91,5.69)	5.03(4.76,5.37)	<0.001
TG(mmol/L)	1.35(0.99,1.86)	1.00(0.74,1.41)	<0.001
TC(mmol/L)	4.59(4.41,5.57)	4.94(4.37,5.66)	0.785
HDL-c(mmol/L)	1.33 (1.18,1.55)	1.60(1.38,1.86)	<0.001
LDL-c(mmol/L)	2.65(2.32,3.03)	2.62(2.28,3.06)	0.449
VFA(cm2)	87.70(68.90,109.80)	87.60(64.68,114.73)	<0.001
PBF(%)	26.80(22.80,30.70)	32.50(28.40,36.30)	<0.001
FFM(kg)	55.54±6.89	39.64±4.29	<0.001
SMM(kg)	31.07±4.15	21.36±2.56	<0.001
TyG	1.29(0.94,1.62)	0.92(0.60,1.32)	<0.001
TG/HDL-c	1.01(0.65,1.50)	0.61(0.43,0.97)	<0.001
New model	7.48(7.07,7.92)	7.01(6.60,7.60)	<0.001

Note: Continuous data were presented as mean ± SD or median (interquartile range).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; SUA, serum uric acid; ALT, alanine transaminase; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; VFA, visceral fat area; PBF, percent body fat; FFM, fat-free mass; SMM, skeletal muscle mass; TyG, triglyceride-glucose index; TG/HDL-c, triglycerides divided by high-density lipoprotein cholesterol; New model, new insulin resistance prediction model.

Comparison of Basic Characteristics and IR in Groups of SUA

To explore the correlations between SUA and IR, the SUA of males and females were further divided into three groups using the tertiles method (Tables 3 and 4).

Table 3 Characteristics of Male Subjects in the Discovery Cohort According to SUA Tertiles

Items	T1	T2	T3	P
N	43	43	43	
Age(years)	36.33±10.93	36.86±10.64	38.83±12.23	0.484
Height(cm)	175.81±6.57	174.19±5.38	172.80±7.27	0.094
Weight(kg)	74.50(69.30,92.30)	82.20(71.00,105.30)	101.70(88.80,114.70)[b]	<0.001
BMI(kg/m2)	25.26(23.40,31.85)	28.08(23.14,34.75)	32.86(29.04,37.52)[b]	<0.001
SBP(mmHg)	130.24±16.07	128.36±18.20	136.57±13.40[b]	0.047
DBP(mmHg)	77.62±11.45	79.29±11.41	84.57±12.82[b]	0.028
Cr(umol/L)	69.00(61.00,74.64)	72.00(65.00,88.00)	75.00(69.00,84.00)	0.036
SUA(μmol/L)	295.00(258.00,318.00)	366.00(358.00,400.00)[a]	498.00(464.00,562.00)[b]	<0.001
AST(U/L)	21.00(18.00,25.10)	22.00(18.00,26.00)	28.00(22.80,39.40)[b]	<0.001
ALT(U/L)	23.00(15.00,36.70)	24.00(20.00,41.70)	47.00(35.50,65.00)[b]	<0.001
FPG(mmol/L)	4.85(4.59,5.30)	4.91(4.50,5.30)	5.03(4.74,5.35)[b]	0.351
HbA1c(%)	5.40(5.30,5.90)	5.40(5.30,5.70)	5.70(5.40,6.00)	0.031
FFA(mmol/L)	0.77(0.57,0.97)	0.81(0.62,1.02)	0.90(0.74,1.05)	0.043
TG(mmol/L)	1.21(0.94,1.78)	1.34(0.92,1.86)	1.93(1.35,3.68)[b]	<0.001
TC(mmol/L)	4.47(4.11,5.07)	4.47(4.05,5.11)	5.05(4.48,5.91)[b]	0.006
HDL-c(mmol/L)	1.32(1.21,1.54)	1.22(1.04,1.42)	1.21(1.02,1.40)	0.029
LDL-c(mmol/L)	2.75(2.47,3.34)	2.90(2.33,3.42)	3.07(2.74,3.72)	0.091
VFA(cm2)	113.43±66.72	130.61±72.57	170.28±58.50[b]	<0.001
PBF(%)	28.71±9.85	30.54±9.62	35.92±7.48[b]	0.001

(*Continued*)

Table 3 (Continued).

Items	T1	T2	T3	P
FFM(kg)	56.43±7.84	59.44±8.44	64.42±7.88[b]	<0.001
SMM(kg)	31.69±4.92	33.50±5.01	36.25±4.85[b]	<0.001
FINS(μU/mL)	11.33(6.87,15.99)	12.43(7.34,16.55)	18.19(13.41,26.66)[b]	<0.001
TyG	1.04(0.77,1.49)	1.11(0.83,1.59)	1.53(1.18,2.23)[b]	<0.001
HOMA-IR	2.50(1.56,4.34)	2.68(1.60,3.90)	4.19(3.05,7.04)[b]	<0.001
Adipo-IR	7.15(4.55,15.75)	9.61(5.26,14.81)	15.95(10.88,29.24)[b]	<0.001
TG/HDL-c	0.91(0.64,1.32)	1.11(0.83,1.80)	1.60(1.02,2.53)[b]	<0.001
New model	7.40(6.67,8.07)	7.63(6.84,8.07)	8.09(7.77.8.36)[b]	<0.001

Notes: [a]T1 VS T2, p<0.05. [b]T2 VS T3, p<0.05.

Table 4 Characteristics of Female Subjects in the Discovery Cohort According to SUA Tertiles

Items	T1	T2	T3	P
N	63	63	63	
Age(years)	34.84±8.81	34.22±10.88	33.73±10.07	0.745
Height(cm)	163.07±6.00	163.90±5.52	162.71±5.73	0.698
Weight(kg)	58.60(52.20,64.00)	81.50(67.80,92.00)[a]	89.40(84.60,99.50)[b]	<0.001
BMI(kg/m2)	21.26(19.72,25.38)	30.56(24.70,34.47)[a]	33.46(31.57,37.46)[b]	<0.001
SBP(mmHg)	118.19±15.17	128.29±16.43[a]	133.92±21.67[b]	0.424
DBP(mmHg)	70.68±10.20	78.95±11.39[a]	81.49±13.38[b]	0.178
Cr(umol/L)	56.00(50.00,66.00)	61.00(54.00,74.00)	58.00(52.75,66.25)	0.016
SUA(μmol/L)	230.00(208,250)	312.00(287.00,340.00)[a]	419.00(385.00,483.00)[b]	<0.001
AST(U/L)	16.00(14.00,20.00)	19.00(16.00,25.20)	30.00(19.60,43.00)[b]	<0.001
ALT(U/L)	13.00(10.00,19.00)	19.00(13.00,30.00)	35.30(19.60,67.10)[b]	<0.001
FPG(mmol/L)	4.80(4.40,5.10)	4.89(4.53,5.31)	5.03(4.58,5.88)[b]	0.025
HbA1c(%)	5.40(5.30,5.60)	5.50(5.40,5.80)	5.70(5.40,6.10)	0.007
FFA(mmol/L)	0.74(0.60,0.95)	0.87(0.63,1.04)[a]	0.90(0.72,1.13)	0.020
TG(mmol/L)	0.90(0.67,1.28)	1.31(0.97,1.75)[a]	1.75(1.39,2.85)[b]	<0.001
TC(mmol/L)	4.57±0.99	4.70±1.02	5.10±0.99b	0.062
HDL-c(mmol/L)	1.66(1.40,1.82)	1.35(1.20,1.80)[a]	1.17(0.97,1.43)[b]	<0.001
LDL-c(mmol/L)	2.70(2.37,3.21)	2,79(2.33,3.28)	3.21(2.57,3.72)[b]	0.003
VFA(cm2)	92.36±45.55	167.78±59.35[a]	204.26±36.53[b]	0.023
PBF(%)	31.18±7.48	41.18±7.38[a]	45.85±4.95	0.023
FFM(kg)	41.19±5.12	42.11±7.46	49.54±5.60	0.358
SMM(kg)	22.14±3.00	25.82±4.44	27.39±3.38	0.376
FINS(μU/mL)	8.91(6.34,14.57)	15.43(10.12,24.20)[a]	19.64(16.20,27.44)[b]	<0.001
TyG	0.73(0.44,1.14)	1.13(0.81,1.50)[a]	1.52(1.18,1.98)[b]	<0.001
HOMA-IR	1.87(1.26,3.30)	3.41(2.12,5.40)[a]	4.47(3.37,7.03)[b]	<0.001
Adipo-IR	5.86(4.40,11.88)	13.76(7.35,19.55)[a]	19.99(13.12,28.11)[b]	<0.001
TG/HDL-c	0.55(0.38,0.83)	0.91(0.58,1.48)[a]	1.42(0.96,2.79)[b]	<0.001
New model	6.75(6.34,7.26)	7.67(2.67,8.00)[a]	8.09(7.65,8.38)[b]	<0.001

Notes: [a]T1 VS T2, p<0.05. [b]T2 VS T3, p<0.05. Continuous data were presented as mean ± SD or median (interquartile range).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; SUA, serum uric acid; AST, aspartate transaminase; ALT, alanine transaminase; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FFA, free fatty acids; TG, triglycerides; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; VFA, visceral fat area; PBF, percent body fat; FFM, fat-free mass; SMM, skeletal muscle mass; FINS, fasting insulin; TyG, triglyceride-glucose index; HOMA-IR, homeostatic model assessment of insulin resistance; Adipo-IR, adipose tissue insulin resistance; TG/HDL-c, triglycerides divided by high-density lipoprotein cholesterol; New model, new insulin resistance prediction model.

In males, there were significant differences in Weight, BMI, ALT, AST, FPG, HbA1c, FFA, TG, TC, HDL-c, FINS, VFA, PBF, FFM, SMM, TyG, HOMA-IR, Adipo-IR, TG/HDL-c and New model among the three groups ($p<0.05$). BMI, ALT, AST, FPG, HbA1c, FFA, TG, FINS, VFA, PBF, FFM, and SMM increased significantly with the tertiles of SUA, and IR was stronger.

In females, there were significant differences in Weight, BMI, ALT, AST, FPG, HbA1c, FFA, TG, HDL-c, LDL-c, FINS, VFA, PBF, TyG, HOMA-IR, Adipo-IR, TG/HDL-c, and New model among the three groups ($p<0.05$). As expected, BMI, ALT, AST, FPG, HbA1c, FFA, TG, LDL-c, FINS, VFA, and PBF increased significantly with the tertiles of SUA, and also IR was stronger.

Correlation Analysis of SUA and IR

The changes of IR alternatives at different SUA levels had led us to think about the association between IR and SUA. As shown in Figure 1, SUA was positively correlated with HOMA-IR, Adipo-IR, TyG, TG/HDL-c and New model in both cohorts ($p<0.001$). And SUA has the strongest correlation with New model. The correlation coefficients were 0.379 and 0.675, respectively, for subjects of different sexes in the Discovery Cohort. In the Verification Cohort, the correlation coefficients were 0.245 and 0.412, respectively.

Association of SUA with IR Risk

Binary Logistic regression was used to analyze the relationship between SUA and IR risk. Adjusting for age, sex, SBP, BMI and HDL-c in the Discovery Cohort, the results showed that HUA could increase the risk of co-existing IR in obese patients. The OR value of HOMA-IR was 2.709 (95% CI, 1.106, 6.635), and the OR value of New model was 3.790 (95% CI, 1.941, 7.398). All results were presented in Table 5.

Discussion

In this study, we retrospectively compared the differences in general clinical indicators and IR in 129 males and 189 females in the Discovery Cohort, and verified the association between SUA and IR in 4333 subjects who underwent physical examination. The results showed a correlation between SUA and IR regardless of sex, and this association was significantly stronger in women than men, more notably, the strongest correlation between IR and SUA as assessed by New model.

In our subjects, the incidence of hyperuricemia and average SUA level were significantly higher among males than females. A survey[17] based on the data from CNHS 2015–2017 has confirmed sex differences in hyperuricemia. Due to differences in SUA between males and females, male and female subjects in the Discovery Cohort were divided into three groups based on SUA. We noticed that as SUA levels increased, lipid values and alternative IR indicators also increased, regardless of sex. Especially in the T3 group, metabolic disorders and insulin resistance were more severe. Previous studies[18] have shown that dyslipidemia, high triglycerides and LDL-C, and low HDL-C, as well as obesity, indicated proinflammatory states/oxidative stress. When the body is in a state of inflammation or oxidative stress, IR is more likely to occur.

A previous cohort study[19] had already shown that patients with elevated SUA were most likely to develop IR and diabetes over years to decades, with each 1 mg/dL increase in SUA associated with a 17% increased risk of T2D. Since insulin mainly binds to cell receptors in skeletal muscle, adipose tissue, and liver,[20] We thoroughly assessed the relationship between SUA and multi-organ IR in different sexes. Similar to the results of a recent Iranian study,[21] TyG and TG/HDL-c were also correlated with SUA in the Two Cohorts of this study. In addition, a study in northern China,[12] which included 5821 adults, found that SUA was associated with HOMA-IR and Adipo-IR regardless of BMI, and highlighted the key role of Adipo-IR in SUA metabolism and hyperuricemia. Unlike previous studies, we innovatively adopted New model to assess the association between insulin resistance and SUA. Surprisingly, regardless of sex, the correlation between SUA and New model was stronger than other IR alternatives in Two Cohort, which may be fundamentally due to its combination of VFA and multiple biochemical indicators. In particular, we observed that the correlation coefficient between SUA and New model in the Discovery Cohort was stronger than that in the Verification Cohort, which further indicated New model could better evaluate IR in people with obesity.

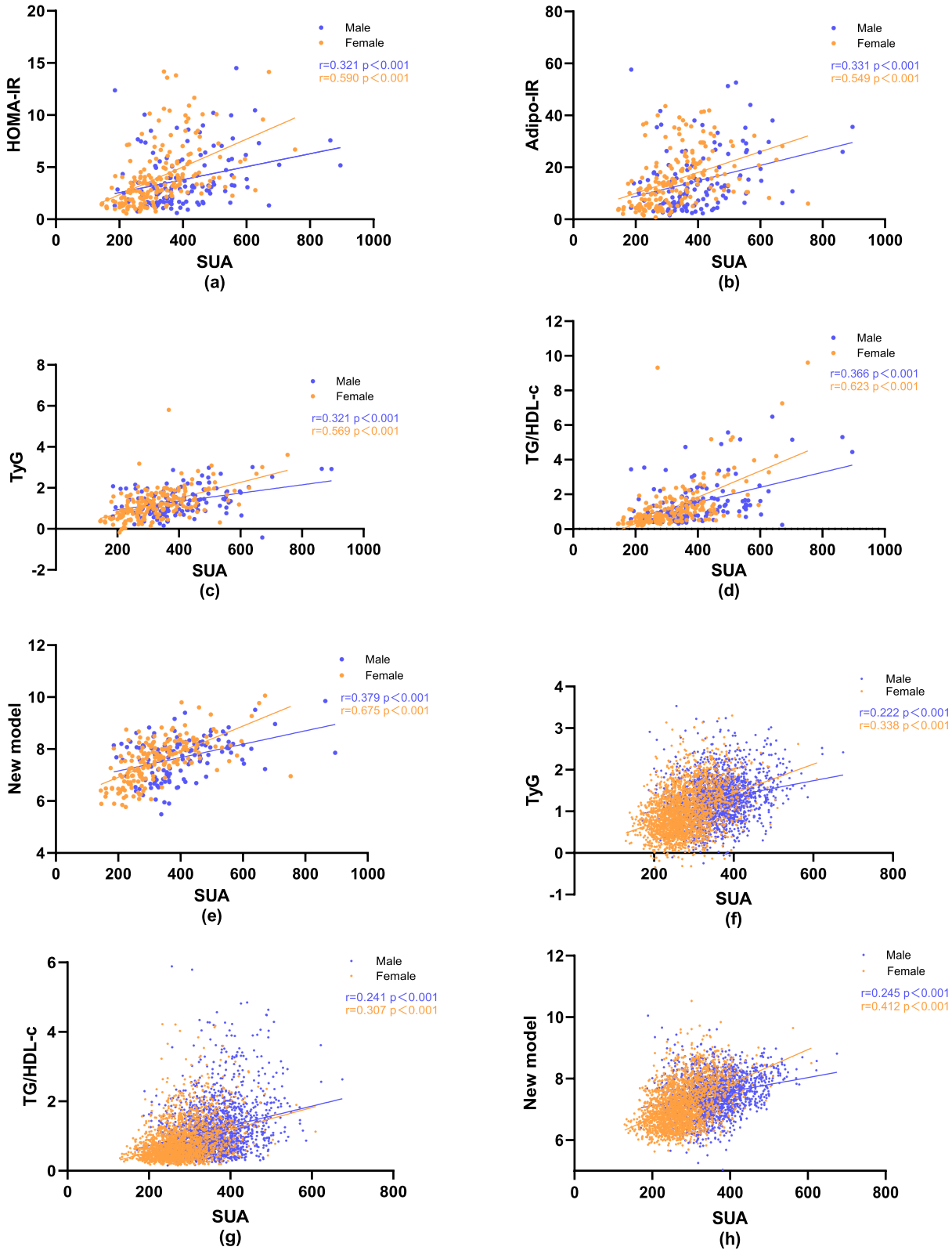

Figure 1 Correlation between insulin resistance and SUA in male and female subjects.

We also found that women had higher FINS levels than men, and the correlation between SUA and IR was stronger in women than in men. We then obtained the same results in a large sample of people in the Verification Cohort. This finding is consistent with previous studies. The US National Health and Nutrition Examination Survey data from 2011 to

Table 5 Association Between SUA and the Risk of IR in the Discovery Cohort

		Model1 OR(95% CI)	Model2 OR(95% CI)	Model3 OR(95% CI)
HOMA-IR	NUA	1	1	1
	HUA	6.204(2,959,13.008)	5.849(2.655,12.887)	2.709(1.106,6.635)
	p	<0.001	<0.001	<0.005
New model	NUA	1	1	1
	HUA	5.783(3.284,10.184)	5.003(2.699,9.275)	3.790(1.941,7.398)
	p	<0.001	<0.001	<0.001

Notes: Model 1: not adjusted. Model 2: adjusted for age, sex, SBP. Model 3: adjusted for BMI and HDL-c based on Model 2.

Abbreviations: OR, odds ratio; CI, confidence interval; NUA, not hyperuricemia; HUA, hyperuricemia; HOMA-IR, homeostatic model assessment for insulin resistance.

2016[22] suggest that the relationship between SUA and IR remains significant after full adjustment for confounding factors. Compared to the lowest quartile of SUA, men and women had an OR of 1.600 and 1.940 in the highest quartile. Furthermore, A cross-sectional study[23] in Brazil that included 13,207 participants, stratified by sex, showed that higher SUA levels were significantly associated with impaired blood sugar status, and this association was stronger in women. The reason for this phenomenon may be related to female estrogen levels,[24] which can directly act on the islet beta cells to promote insulin synthesis, increase glucose-stimulated insulin secretion, and promote urinary excretion. However, it is not known whether estrogen plays a decisive role in our study.

Recently, three Mendelian randomization studies have demonstrated that genetic loci associated with SUA can predict SUA levels but do not predict T2D, suggesting that they do not play a causal role.[25–27] Therefore, we cannot determine whether SUA can directly cause IR. Adipokines released by adipose tissue affect insulin sensitivity in other tissues, especially skeletal muscle, and liver, leading to local and systemic IR.[28] These findings also explained the significant decrease in the OR values of both HOMA-IR and the new model after adjusting for confounding factors such as BMI. Moreover, we noted that females with HUA had significantly higher VFA and PBF than males, New model containing VFA were most strongly associated with SUA, and SUA was more strongly associated with IR in people with obesity, and we hypothesized that obesity also strengthened the association between SUA and IR.

While the exact causal relationship between SUA and IR remains unclear, numerous mechanistic studies have elucidated that SUA has the potential to cause IR. High SUA may inhibit IRS1 and Akt insulin signaling and induce IR.[4] SUA inhibits the initiation of the insulin signaling pathway by recruiting ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) at the receptor level. In the liver, HUA can lead to hepatic insulin resistance through the above pathways.[29] Excessive SUA will reduce the bioavailability of nitric oxide, leading to endothelial dysfunction and IR, and then cause IR in tissues with wide distribution of endothelial cells such as kidney and cardiovascular.[30] SUA promotes oxidative stress and increases the production of pro-inflammatory cytokines, and can induce IR in a variety of tissues and cells, including pancreatic beta cells, skeletal muscle, adipose tissue, liver, cardiac vascular endothelial cells, and macrophages.[7]

There are some limitations in this study. The standard method for measuring insulin resistance is the normal glucose hyperinsulinemic clamp technique, which is widely considered the most reliable. However, due to its intricate and invasive nature, it was not applied in this study, leading to an insufficiently accurate assessment of IR. Secondly, no information was obtained on factors that influence SUA, such as the subjects' eating habits and exercise. Although we obtained the strongest correlation between New model and SUA, we could only compare the New model with TyG and HDL-c in the Verification Cohort, because FINS and FFA were not detected in the physical examination population. Therefore, these findings should be supported by broader studies, such as prospective cohort studies, and studies of different ethnic groups and mechanisms.

Conclusions

Our study supports a positive correlation between SUA and IR, and the correlation between SUA and New model is stronger than other IR alternatives. In addition, the analysis showed that there was a positive correlation between SUA and IR in both men and women, and the correlation was significantly stronger in women than in men. Despite this, the causal relationship between SUA and IR remains to be established. Further prospective cohort studies are necessary, such as including larger sample data and other ethnic groups, while controlling for confounding factors such as BMI and sex.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors participating in this study declare that they have no conflicts of interest.

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