

Fractional Excretion of Urate is Positively Associated with Type 2 Diabetes in HUA Patients: A Cross-Sectional Study

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Purpose: People with hyperuricemia (HUA) are often related to metabolic disorders such as diabetes, metabolic syndrome (MetS), and obesity. However, the correlation between excretion of uric acid and these diseases is unclear. Our study aimed to explore the relationship between uric acid excretion and type 2 diabetes (T2D).

Methods: A total of 228 HUA patients from Tianjin Medical University General Hospital from 2022 to 2023 were included in this study. We collected demographic, biochemical, and anthropometric data on each subject. Urine uric acid excretion (UUAЕ) was calculated enzymatically from a single urine collection that lasted 24 hours. And fractional excretion of uric acid (FEUA) was calculated from serum uric acid and creatinine and uric acid and creatinine. Binary logistic regression modeling assessed the association between uric acid excretion and T2D.

Results: Of the 228 subjects, 13.4% had T2D and 48.7% had obesity. The obesity group had a lower FEUA ($p < 0.05$) and a higher UUAЕ compared to the control group ($p < 0.05$). And FEUA had a stronger correlation with the risk of T2D ($p < 0.001$). Also, there was a negative association between BMI and FEUA and a positive link between BMI and UUAЕ in the outpatients.

Conclusion: Increased FEUA levels were significantly associated with T2D in HUA patients. Therefore, routine calculating of FEUA is essential for proper diagnosis and appropriate treatment T2D of in HUA patients.

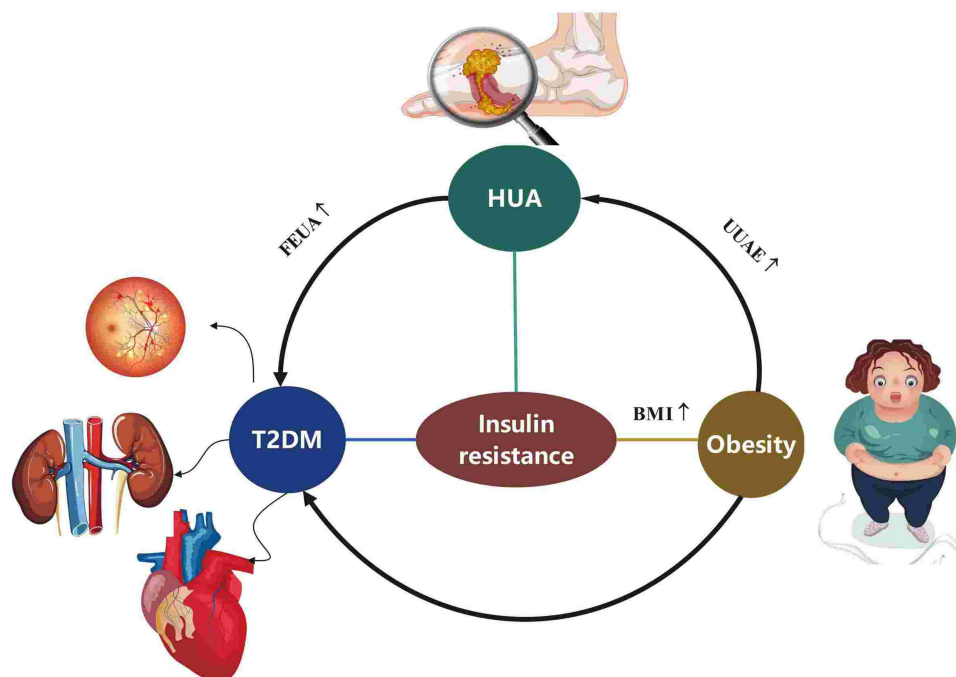
Keywords: urine uric acid excretion, hyperuricemia, obesity, Type 2 diabetes, fractional excretion of urate

Introduction

HUA constitutes a metabolic disorder primarily attributed to disturbances in purine metabolism, which the prevalence of in Chinese adults was 14.0%.¹ In humans, purines are ultimately metabolized into uric acid, which can further convert uric acid into allantoin by the enzyme uricase, readily excretable through urine. However, the enzyme uricase is absent in the human body.² The kidneys play a pivotal role in regulating amounts of uric acid in the circulation. Nearly two-thirds of uric acid goes away via the kidneys, while the remaining one-third leaves the body through the intestinal tract uricolysis.³ Renal capacity, though, is finite. HUA may arise from a disturbance in the balance between the production and excretion of uric acid.

All the time, research is being done on the link between serum uric acid (SUA) and several metabolic disorders, including diabetes,^{4,5} hypertension,^{6,7} obesity,⁸ metabolic syndrome,⁹ dyslipidemia,¹⁰ kidney dysfunction,¹¹ liver dysfunction,¹² and cardiovascular disease.¹³ A prospective study demonstrated that higher SUA levels increase the risk of developing diabetes.¹⁴ Recently lower cut-offs for HUA have been defined since they are more strongly associated with CV diseases. HUA was diagnosed both with the classic cut-off of 6.0 mg/dl for females and 7.0 mg/dl for males, but also with the newly identified one in the URRAH (Uric Acid Right for Heart Health) study that is 5.1 mg/dl for females and 5.6 mg/dl for males.¹⁵ The threshold of 5.6 mg/dl previously proposed by the URRAH Study Group, is predictive of an increased risk of total and CV mortality in people with diabetes.¹⁶ The newly reported URRAH cutoff values for HUA better relate to atherogenic lipoprotein (LDL and

Graphical Abstract



non-HDL) when compared to the classic one.¹⁷ Also, treating hyperinsulinemia and diabetes-related insulin resistance with troglitazone or a low-energy diet in overweight hypertensive patients lowers serum UA levels.¹⁸ Additionally, several publications have shown the independent impact of SUA on the onset of MetS and hypertension in Chinese hospitalized type 2 diabetic patients.¹⁹ A population-based longitudinal epidemiological investigation found a link between raised concentrations of SUA and an elevated risk of obesity.²⁰ In healthy patients, a prior Chinese study likewise revealed a favorable correlation between BMI and SUA.²¹ Overall, these investigations repeatedly show that higher SUA levels are strongly associated with metabolic problems in individuals with and without diabetes.

The UUA test is commonly employed in clinical practice as a non-invasive method to quantify uric acid excretion levels. Elevated SUA levels typically coincide with heightened uric acid concentrations in urine. Despite multiple studies investigating the connections of SUA with diabetes, MS, and obesity, there exists an absence of data concerning the associations between UUA, FEUA, and diabetes in populations with HUA. A few studies looked into the link between FEUA and the development of simple renal cysts²² and gout.²³ In both men and postmenopausal women with type 2 diabetes, HUA and high levels of FEUA were independent risk factors for the growth of simple renal lesions.²² Further, higher excretion of urine uric acid was linked to lower SUA levels during the acute gout flare.²³ However, among populations with HUA, the relationship between uric acid excretion and T2D has not yet been studied. Therefore, our primary aim is to explore the association between uric acid excretion and T2D in Chinese outpatients with HUA.

Methods and Materials

Subjects

The study included 228 patients with HUA in total. Between 2022 and 2023, Tianjin Medical University General Hospital attracted outpatients (Figure 1). The following were the exclusion criteria: 1) a history of severe hypoglycemia, type 1 diabetes, other kinds of diabetes, or acute complications of diabetes; 2) Use of drugs affecting uric acid excretion, including diuretic, losartan, aspirin, glucocorticoids, cyclosporine, immunosuppressive agents, anti-tuberculosis drugs, sodium bicarbonate,

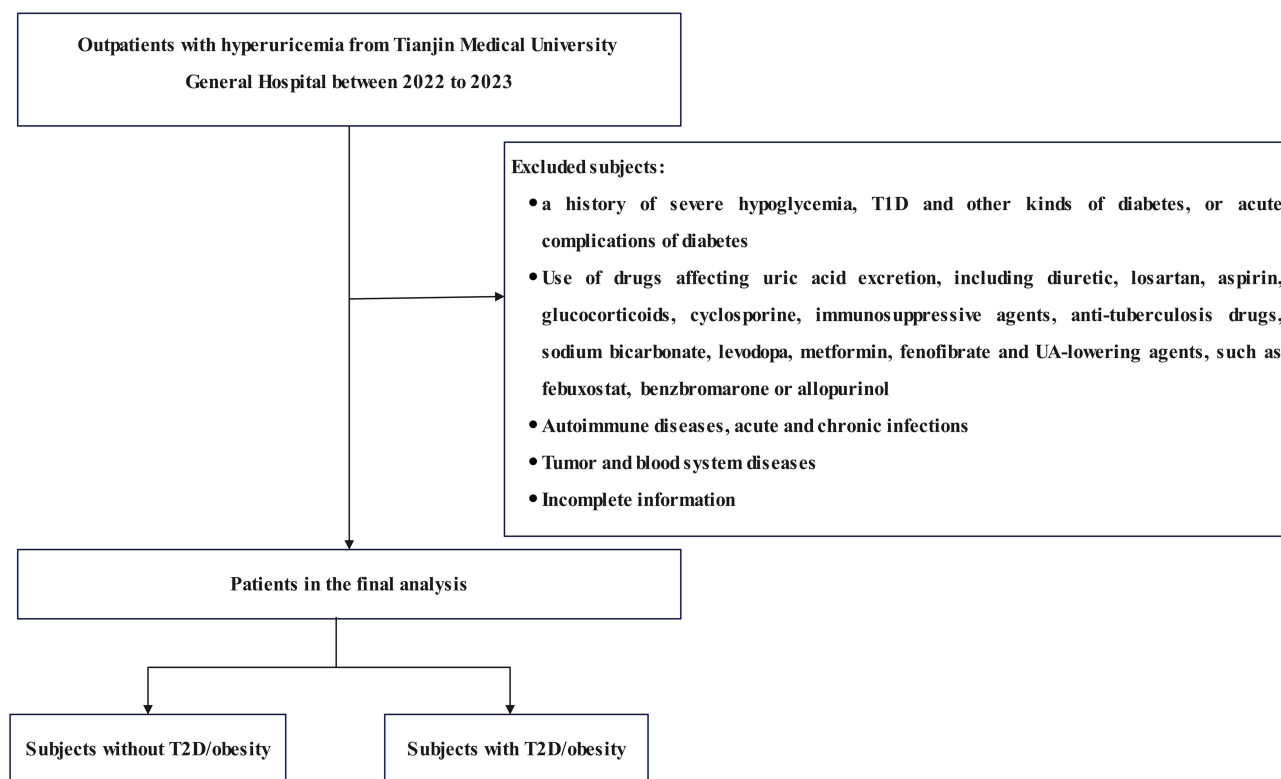


Figure 1 Flowchart of the cross-sectional study.

levodopa, metformin, fenofibrate and UA-lowering agents, such as febuxostat, benzbromarone or allopurinol²⁴; 3) Autoimmune diseases, acute and chronic infections; 4) Tumor and blood system diseases; 5) Incomplete information.

Definition

HUA was defined differently in males and females; SUA levels >7.0 mg/dL (420 mol/L) in males and SUA levels 6.0 mg/dL (360 mol/L) in females.²⁵ The 1999 World Health Organization standard served as a basis for the diagnosis of T2D.²⁶ Following the criteria established for the Chinese population, individuals with a Body Mass Index (BMI) of 28 or greater are classified as obese.²⁷ And weight (kg) / height (m^2) was used to compute BMI. Additionally, formula $[100 \times UUE \times Scr / (SUA \times \text{urine creatinine})]$ was used to compute the fractional excretion of urate (FEUA).²⁸ Based on the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the estimated glomerular filtration rate (eGFR) was determined.²⁹ EGFR above the upper quartile of all study subjects, that is, $EGFR > 112 \text{ mL/min} \cdot 1.73 \text{ m}^2$, was defined as glomerular hyperfiltration group (GH) and $<112 \text{ mL/min} \cdot 1.73 \text{ m}^2$ as a glomerular non-hyperfiltration group (non-GH).

Data Collection

All subjects' demographic information was gathered, including the subject's gender, age, previous diagnosis of hypertension, or diabetes, the length of their HUA, and any comorbidities (including gout and renal calculi) associated with it. Outpatient staff measured anthropometric indicators including weight and height. All subjects were on a normal purine diet for at least 3 days before collecting blood and urine samples. Venous blood specimens were obtained after overnight fasting to measure the serum concentrations of the fasting plasma concentrations of glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (GGT), creatinine (Cr), and uric acid (UA) using a type ARCHITECT i2000 immunoassay analyzer (Abbott, America). A single 24-hour urine sample was collected for measuring the 24-hour urine uric

acid, creatinine, and microalbuminuria using a type IMMULITE 2000 XPi Immunoassay System (Siemens Healthineers, Germany).

Statistical Analysis

We used IBM SPSS Statistics (version 26) to analyze the data. Data normality was evaluated using the nonparametric Kolmogorov–Smirnov (K-S) test. While categorical data were shown as percentages (%), continuous variables were given as either the mean standard deviation (SD) or the median with an interquartile range (25%, 75%). The comparison of normally distributed variables among groups was carried out using the independent sample t-test and one-way analysis of variance. Additionally, to compare data that is not normally distributed between groups, the Mann–Whitney U-test and the Kruskal–Wallis H-test were done. Categorical variables are presented as percentages and the Chi-square test was used to look for group differences. Utilizing Spearman correlation analysis, the links between UUAЕ, FEUA, and other factors were evaluated. To examine the relationships between FEUA and illnesses, logistic regression calculations were applied.

Results

Baseline Characteristics

Tables 1 and 2 exhibits the clinical and biochemical features of the individuals. Compared with non-diabetes, participants with diabetes were older than non-diabetes ($p=0.001$). Participants with diabetes presented with a higher volume of urine, urine uric acid excretion (UUAЕ), urine creatinine excretion (UCE), and higher levels of TG ($p=0.016$), FPG ($p<0.001$), and TC ($p=0.025$). They also showed lower levels of fractional excretion of urate than the non-diabetes individuals

Table 1 General Characteristics of the Study Population

	Non-Diabetes (n=201)	Diabetes (n=27)	p	Non-GH (n=169)	GH (n=59)	p
Age (years)	37(30,46)	43(39,60)	0.001	40(34,51)	31(26,39)	<0.05
Duration (years)	3(1,5)	3(1,7)	0.465	3(1,5)	2(0,8,5)	0.041
BMI (kg/m ²)	27.78(24.8,30.5)	27.55(25.61,31.41)	0.800	27.47(25.1,30.31)	28.47(24.93,31.86)	0.20
TG (mmol/L)	2.11(1.65,2.94)	2.73(1.99,3.63)	0.016	2.14(1.66,2.91)	2.23(1.75,3.22)	0.39
TC (mmol/L)	5.01±1.13	5.03±1.19	0.025	4.99±1.11	5.10±1.22	0.497
LDL (mmol/L)	3.25(2.75,3.83)	3.09(2.69,3.68)	0.348	3.26±0.83	3.37±0.98	0.421
HDL (mmol/L)	1.06(0.97,1.21)	1.06(1,1.17)	0.792	1.06(0.98,1.21)	1.04(0.95,1.23)	0.97
ALT (U/L)	35(23,5,47)	34(24,48)	0.796	34(23,45)	37(27,64)	0.119
AST (U/L)	24(18,29,5)	24(18,33)	0.521	25(18,30)	23(18,29)	0.785
GGT (U/L)	28(18,51)	21(16,47)	0.357	25(18,46,5)	36(17,60)	0.11
FPG (mmol/L)	5.1(4.8,5.45)	6.9(6.2,7.5)	<0.001	5.1(4.9,5.6)	5.2(4.7,5.5)	0.402
Volume of urine (mL)	2200(1725,3000)	2634(2000,3000)	0.714	2300(1790,3000)	2100(1600,3000)	0.273
UUAЕ (mg/24h)	672.9(520.45,883.43)	747(555.06,893.25)	0.643	695.3(525.12,883.43)	638.1(499.5,890.78)	0.553
UCE (mg/24h)	1853.4(1405.35,2259.18)	1606.15(1114.10,2010.96)	0.053	1854.78(1405.35,2259.18)	1732.39(1299.76,2209.75)	0.223
SUA (umol/L)	523.55±108.68	491.22±90.62	0.141	514.17±102.65	535.64±118.21	0.185
Cr (umol/L)	77(70,86)	74(68,89)	0.245	80(74,5,90)	68(63,71)	<0.05
eGFR (mL/min/1.73m ²)	109.79±21.24	106.97±17.94	0.51	104.31(92.04,113.19)	131.09(127.28,137.49)	<0.05
FEUA (%)	3.79(3.03,4.68)	4.59(3.57,6.42)	0.006	4.09(3.26,5.02)	3.19(2.73,3.84)	<0.05
Gender (male, %)	185(92%)	22(81.5%)	0.084	158(93.5%)	49(83.1%)	<0.05
Hypertension (yes, %)	35(17.4%)	7(25.9%)	0.294	37(21.9%)	5(8.5%)	<0.05
hyperlipidemia (yes, %)	63(31.3%)	12(44.4%)	0.174	49(29%)	26(44.1%)	<0.05
Underexcreted-HUA (yes, %)	152(75.6%)	15(55.6%)	0.027	123(72.8%)	44(74.6%)	0.79
Obesity (yes, %)	99(49.3%)	12(44.4%)	0.639	77(45.6%)	34(57.6%)	0.11
Gout (yes, %)	159(79.1%)	15(55.6%)	<0.05	132(78.1%)	42(71.2%)	0.28

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUAЕ, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

Table 2 General Characteristics of the Study Population

	Non-Obesity (n=117)	Obesity (n=111)	p	Non-Underexcretion Hyperuricemia (n=61)	Underexcretion Hyperuricemia (n=167)	p
Age (years)	40(31.5,52.5)	36(30,44)	<0.05	40(34.5,54)	37(30,46)	0.063
Duration (years)	3(1,5)	3(1,5.5)	0.95	3(1,5.75)	3(1,5)	0.605
BMI (kg/m ²)	25.18(23.9,26.43)	30.52(29.37,33.95)	<0.05	28.25(25.54,31.23)	27.7(24.8,30.48)	0.513
TG (mmol/L)	2.11(1.61,2.835)	2.22(1.76,3.05)	0.255	2.22(1.68,3.17)	2.13(1.66,2.94)	0.691
TC (mmol/L)	4.81±1.06	5.23±1.18	<0.05	5.25±1.14	4.93±1.13	0.056
LDL (mmol/L)	3.19(2.75,3.575)	3.35(2.69,4.03)	<0.05	3.29(2.75,3.95)	3.22(2.71,3.75)	0.245
HDL (mmol/L)	1.08(0.99,1.21)	1.05(0.96,1.21)	0.304	1.08(1,1.23)	1.06(0.97,1.21)	0.815
ALT (U/L)	32(22,43)	39(29,53)	0.002	33(23.5,44.5)	36(24,48)	0.081
AST (U/L)	23(18,30)	25(18,30)	0.453	23(18,28)	25(18,30)	0.303
GGT (U/L)	22(17,47)	34(20,54)	0.013	23(16,55)	28(18,51)	0.172
FPG (mmol/L)	5.1(4.8,5.6)	5.1(4.8,5.5)	0.659	5.3(4.85,5.85)	5.1(4.8,5.5)	0.166
Volume of urine (mL)	2200(1725,3000)	2230(1750,3000)	0.519	2500(1775,3500)	2200(1700,3000)	0.691
UUAЕ (mg/24h)	627.13(470.6,787.555)	768(572.4,1023.04)	<0.05	1056.72(666.98,1263.3)	627.6(496.1,770.7)	<0.001
UCE (mg/24h)	1660.2(1265.62,1949.465)	2058.59(1606.15,2429)	<0.05	2083.57(1228.35,2797.94)	1796.25(1404.9,2119.2)	0.031
SUA (umol/L)	502.42±105.47	537.96±106.11	<0.05	480.49±107.92	534.05±103.37	0.001
Cr (umol/L)	78(70,89)	76(69,82)	0.203	76(70,87.5)	77(70,86)	0.957
eGFR (mL/min/1.73m ²)	106.44±20.77	112.64±20.57	<0.05	5.25±1.14	4.93±1.13	0.642
FEUA (%)	4%(3.18%,5.16%)	3.73%(2.94%,4.59%)	<0.05	5.67(4.4,6.72)	3.54(2.89,4.19)	<0.001
Gender (male, %)	102(87.2%)	105(94.6%)	0.053	54(88.5%)	153(91.6%)	0.475
Hypertension (yes, %)	20(17.1%)	22(19.8%)	0.596	15(24.6%)	27(16.2%)	0.146
hyperlipidemia (yes, %)	37(31.6%)	38(34.2%)	0.675	24(39.3%)	51(30.5%)	0.21
Gout (yes, %)	87(74.4%)	87(78.4%)	0.476	24(39.3%)	51(30.5%)	0.875
Diabetes (yes, %)	15(12.8%)	12(10.8%)	0.639	12(19.7%)	15(9%)	0.224

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUAЕ, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

($p=0.006$, Figure 2). The prevalence of underexcretion HUA was lower in the Diabetes group ($p=0.027$). Participants with GH presented with lower FEUA and Cr ($p<0.05$). The prevalence of hypertension was higher in the non-GH group ($p<0.05$). The prevalence of HUA was lower in the non-GH group ($p<0.05$). Tables 3 and 4 provided a snapshot of the general characteristics of the study's participants according to the quartile of UUAЕ, and FEUA (%). In Table 3, compared to Q1–Q2, the BMI of Q4 was higher ($p<0.001$), and Q3 had a higher BMI than Q1. For each additional unit of ALT, there is a difference between the groups ($p=0.007$).

In Table 3 according to UUAЕ quartiles, the prevalence rate of obesity was 35.1%, 43.9%, 49.1%, and 66.7% in the Q1–Q4 group. And the prevalence rate of T2D was 10.5%, 10.5%, 14.0%, and 12.3% in the Q1–Q4 group. The prevalence of obesity was higher in the fourth quarter group than in the Q1–Q2 group ($p<0.05$, Figure 3A). The incidence of hyperlipidemia was higher in the Q3–Q4 group than in the Q2 unit and the Q3 group than the Q1 group ($p=0.012$). However, no appreciable variations were found in age, TG, TC, HDL, LDL, AST, GGT, FPG, SUA, Cr, or eGFR, and there was no discernible difference in the incidence of diabetes or MetS across the four groups ($p>0.05$).

In Table 4, according to FEUA quartiles, the prevalence rate of obesity was 56.1%, 51.7%, 50%, and 36.8% in the Q1–Q4 group. And the prevalence rate of T2D was 7%, 8.6%, 12.5%, and 19.3% in the Q1–Q4 group. There was a substantial variance in patient age between the Q4 and Q2–Q3 groups ($p<0.001$), as well as between the Q3 and Q1 groups. Q4's FPG was higher than the one for Q1–Q3's ($p<0.05$). Likewise, the Q4 group's SUA levels were lower than the Q1–Q3 group's ($p<0.05$, Figure 3B), and the Q2–Q3 group's SUA levels were lower than the Q1 group's ($p<0.05$, Figure 3B). But there were no appreciable variations in TG, TC, HDL, LDL, AST, ALT, GGT, the volume of urine, gender, and the incidence of obesity, MetS, gout, and diabetes in the four groups ($p>0.05$).

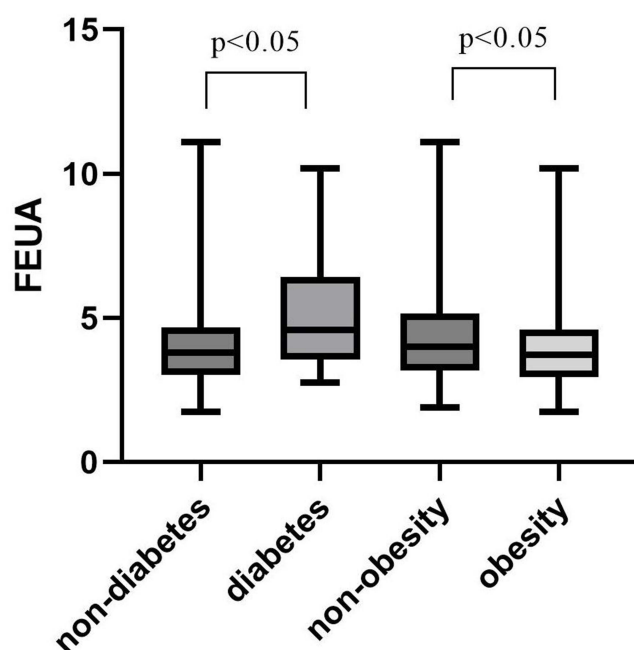


Figure 2 Comparison of FEUA levels between the patients with and without T2D and obesity.

Relationships Between UUAЕ, FEUA, and Other Variables

The correlations between FEUA, UUAЕ, and other factors are displayed in [Tables 5](#) and [6](#). UUAЕ is strongly positively correlated with BMI ($r = 0.353$, $p < 0.001$), SUA ($r = 0.143$, $p < 0.001$), urine volume ($r = 0.304$, $p < 0.001$), and UCE ($r = 0.770$, $p < 0.001$). Yet, there is a substantial inverse relationship ($r = -0.139$, $p = 0.036$) between age and UUAЕ. There is a substantial positive relationship between FEUA and age ($r = 0.402$, $p < 0.001$), FPG ($r = 0.135$, $p < 0.001$), and Cr ($r = 0.235$, $p < 0.001$). There is a substantial negative correlation between FEUA and BMI ($r = -0.159$, $p < 0.001$), UCE ($r = -0.144$, $p < 0.001$), SUA ($r = -0.493$, $p < 0.001$), and eGFR ($r = -0.349$, $p < 0.001$).

Table 3 Characteristics of the Patients According to UUAЕ Quartiles

	Q1	Q2	Q3	Q4	p
Age (years)	42(33,58.5)	36(28.5,47.5)	39(31,48)	37(31,43)	0.061
Gender (male, %)	48(84.2%)	50(87.7%)	56(98.2%)	53(93%)	0.052
Duration (years)	37(31,43)	3(1,5)	2(1,6)	3(1.5,5.5)	0.588
BMI (kg/m ²)	25.88(24.22,28.74)	27.55(24.22,30.45)	27.99(25.83,31.56) ^{&}	29.11(26.96,32.25) ^{&*}	<0.001
TG (mmol/L)	2.16(1.65,2.98)	2.13(1.63,2.8)	2.28(1.81,3.2)	2(1.68,2.98)	0.479
TC (mmol/L)	5.01±1.11	4.84±1.18	5.1±0.97	5.11±1.27	0.581
LDL (mmol/L)	3.3(2.7,3.81)	3.13(2.77,3.72)	3.22(2.81,3.8)	3.29(2.61,3.94)	0.935
HDL (mmol/L)	1.05(0.97,1.22)	1.08(1,1.23)	1.04(0.96,1.16)	1.08(0.99,1.23)	0.696
ALT (U/L)	29(20,41.5)	34(25.5,45.5)	39(26,57.5) ^{&}	40(28,53.5) ^{&}	<0.05
AST (U/L)	23(18,28.5)	25(18.5,29.5)	25(18,31)	25(18.5,29.5)	0.787
GGT (U/L)	24(18.5,41.5)	23(18,48)	31(17.5,51)	33(17,56.5)	0.711
FPG	5.2(4.8,5.6)	5.3(4.9,5.6)	5.2(4.8,5.6)	5.1(4.75,5.5)	0.49
Volume of urine (mL)	2000(1450,2750)	2200(1682,2775)	2500(1937.5,3450) ^{&}	2500(2000,3600) ^{&}	<0.05
UUAЕ (mg/24h)	414.63(342.9,466.97)	582.92(563.2,632.2) ^{&}	770.66(723.14,816.26) ^{&*}	1064.25(984.07,1269.55) ^{&*#}	<0.001
UCE (mg/24h)	1167.2(946.04,1560.73)	1720.37(1378,1896.9) ^{&}	1972.95(1706.68,2246.51) ^{&*}	2475.72(2167.96,3022.28) ^{&*#}	<0.001
SUA (μmol/L)	491.28±126.45	522.46±98.72	538.4±94.52	526.75±102.67	0.109
Cr (μmol/L)	76(69.5,90.5)	78(67.5,88)	77(71,86)	76(70,82.5)	0.971

(Continued)

Table 3 (Continued).

	Q1	Q2	Q3	Q4	P
eGFR (mL/min/1.73m ²)	105.28±21.86	111.66±25.07	108.51±17.47	112.4±17.86	0.244
FEUA (%)	3.55(2.87,4.56)	3.66(2.89,4.65)	3.8(3.1,4.66)	4.47(3.73,5.32) ^{&*}	<0.05
Hypertension (yes, %)	10(17.5%)	8(14%)	12(21.1%)	12(21.1%)	0.733
hyperlipidemia (yes, %)	14(24.6%)	12(21.1%)	26(45.6%) ^{&*}	23(40.4%) [*]	0.012
Gout (yes, %)	41(71.9%)	45(78.9%)	47(82.5%)	41(71.9%)	0.454
MetS (yes, %)	16(28.1%)	16(28.1%)	23(40.4%)	24(42.1%)	0.222
Diabetes (yes, %)	6(10.5%)	6(10.5%)	8(14%)	7(12.3%)	0.927
Obesity (yes, %)	20(35.1%)	25(43.9%)	28(49.1%)	38(66.7%) ^{&*}	<0.05
Underexcreted-HUA (yes, %)	50(87.7%)	49(86%)	49(86%)	19(33.3%)	<0.05

Notes: Compared with Q1 group, [&]p<0.05; compared with Q2 group, ^{*}p<0.05; compared with Q3 group, [#]p<0.05.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUA, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

Table 4 Characteristics of the Patients According to FEUA Quartiles

	Q1	Q2	Q3	Q4	P
Age (years)	31(27.5,40)	36(30,41.5)	40(34.25,50.75) ^{&}	46(37.5,60) ^{&*}	<0.001
Duration (years)	3(1,5)	2.5(1,5)	3(1,6)	3(1,5.5)	0.729
BMI (kg/m ²)	29.07(25.59,31.02)	28.37(24.56,31.07)	27.87(25.37,31.46)	26.7(24.5,28.41)	0.073
TG (mmol/L)	2.46±1.02	2.46±1.53	2.78±1.81	2.55±1.98	0.695
TC (mmol/L)	4.94(4.35,5.75)	4.96(4.23,5.37)	5.08(4.13,5.94)	5(4.53,5.74)	0.765
LDL (mmol/L)	3.31(2.67,3.92)	3.19(2.69,3.48)	3.24(2.74,4)	3.28(2.75,3.77)	0.724
HDL (mmol/L)	1.09(0.97,1.21)	1.03(0.96,1.18)	1.06(0.96,1.21)	1.08(1,1.25)	0.275
ALT (U/L)	35(22,49)	36(25,50.25)	42(30,50.5)	30(22,42.5)	0.073
AST (U/L)	24(18,30.5)	23.5(18.75,30)	27(21.5,30)	23(17,28)	0.086
GGT (U/L)	34(18.5,54.5)	23(18.75,49.5)	31(18.51,75)	21(15.5,50)	0.24
FPG (mmol/L)	5.1(4.8,5.5)	5.1(4.7,5.53)	5.1(4.8,5.4)	5.4(5.5,85) ^{&*}	<0.05
Volume of urine	2000(1682,2705)	2250(2000,3000)	2555(1931.25,3475)	2130(1500,3000)	0.07
UUA (mg/24h)	585.31(439.71,766.9)	649.61(528.38,831.3)	744.2(561.74,955.29) ^{&}	747(532.33,1011.21) ^{&}	<0.05
UCE (mg/24h)	1842.29(1479.21,2322.7)	1936.82(1565.27,2242.75)	1872.24(1474.5,2343.5)	1605.45(1073.36,2042.16) ^{&}	<0.05
SUA (umol/L)	587.49±113.44	534.79±82.83 ^{&}	506.41±85.31 ^{&}	449.7±96.78 ^{&*}	<0.05
Cr (umol/L)	73(66,79.5)	76.5(65,86)	78.5(73,86.75) ^{&}	79(71,95) ^{&}	<0.05
eGFR (mL/min/1.73m ²)	119.76±18.83	113.03±20.06	105.07±17.47 ^{&}	99.84±21.56 ^{&*}	<0.05
Gender (male, %)	52(91.2%)	54(93.1%)	53(94.6%)	48(84.2%)	0.228
Hypertension (yes, %)	7(12.3%)	10(17.2%)	9(16.1%)	16(28.1%)	0.156
hyperlipidemia (yes, %)	15(26.3%)	19(32.8%)	24(42.9%)	17(29.8%)	0.275
Gout (yes, %)	44(77.2%)	42(72.4%)	44(78.6%)	44(77.2%)	0.874
MetS (yes, %)	17(29.8%)	18(31%)	21(37.5%)	23(40.4%)	0.585
Diabetes (yes, %)	4(7%)	5(8.6%)	7(12.5%)	11(19.3%)	0.179
Underexcreted-HUA (yes, %)	54(94.7%)	50(86.2%)	47(83.9%)	16(28.1%) ^{&*}	<0.05
Obesity (yes, %)	32(56.1%)	30(51.7%)	28(50%)	21(36.8%)	0.193

Notes: Compared with Q1 group, [&]p<0.05; compared with Q2 group, ^{*}p<0.05; compared with Q3 group, [#]p<0.05.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUA, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

Association Between FEUA and Diabetes

Table 7 shows the relationship between FEUA and Diabetes. In model 1, we found that a unit increase in FEUA (OR=1.428, 95% CI=1.134–1.799) was significantly associated with the risk of T2D (p=0.002). Model 2's age, duration,

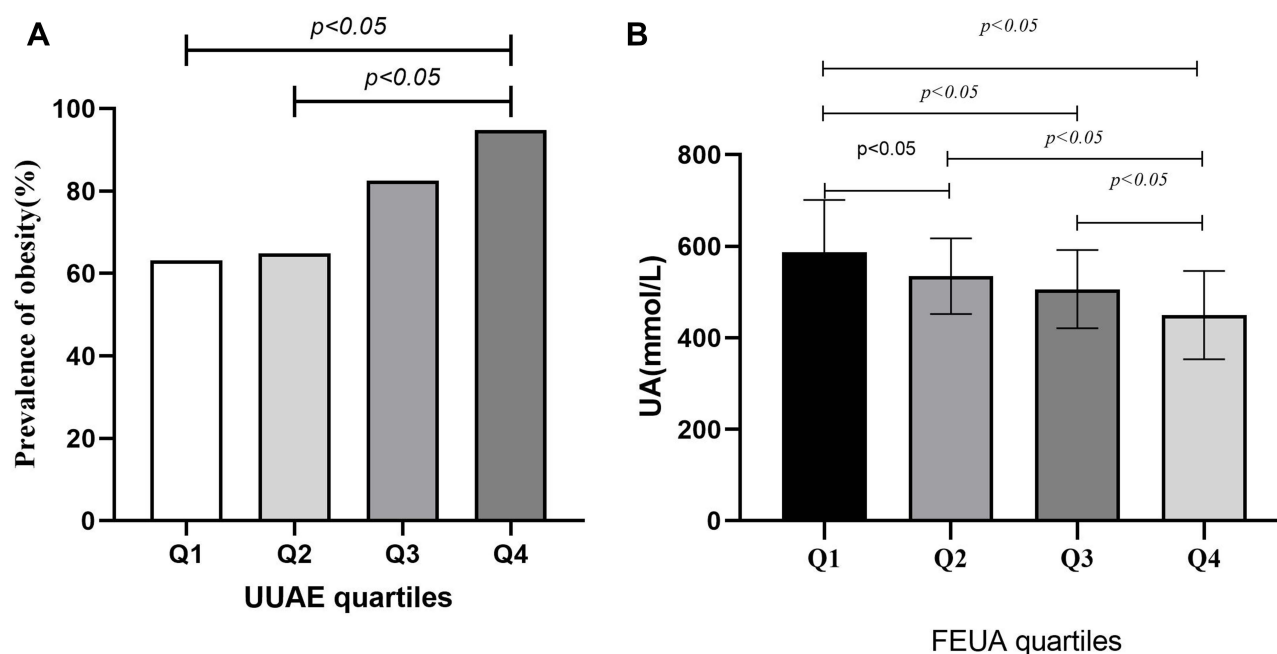


Figure 3 (A) Prevalence of obesity stratified by UUAЕ quartile in HUA. (B) Comparison of UA levels stratified by FEUA quartile in HUA.

gender, and BMI corrections did not change the association between FEUA and the risk of T2D ($p=0.04$). After adjusting for TG, TC, LDL, HDL, SUA, Cr, volume of urine, glomerular hyperfiltration (GH), and hypertension in model 3, FEUA was still linked to an elevated risk of T2D (OR=1.512, 95% CI=1.083–2.111, $p=0.015$).

Table 5 Relationships Between UUAЕ and Other Variables

Variables	r	p
Age (years)	−0.139	0.036
Duration (years)	−0.019	0.78
BMI (kg/m ²)	0.353	<0.001
TG (mmol/L)	0.025	0.713
TC (mmol/L)	0.074	0.264
LDL (mmol/L)	0.037	0.577
HDL (mmol/L)	−0.01	0.882
ALT (U/L)	0.207	0.002
AST (U/L)	0.026	0.697
GGT (U/L)	0.037	0.575
FPG (mmol/L)	−0.07	0.291
Volume of urine (mL)	0.304	<0.001
UCE (mg/24h)	0.770	<0.001
SUA (μmol/L)	0.143	0.031
Cr (μmol/L)	−0.042	0.532
eGFR (mL/min/1.73m ²)	0.097	0.146

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUAЕ, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

Table 6 Relationships Between FEUA and Other Variables

Variables	r	p
Age (years)	0.402	<0.001
Duration (years)	0.034	0.607
BMI (kg/m ²)	−0.159	0.016
TG (mmol/L)	0.014	0.831
TC (mmol/L)	0.053	0.423
LDL (mmol/L)	−0.008	0.909
HDL (mmol/L)	0.051	0.443
ALT (U/L)	−0.047	0.478
AST (U/L)	−0.078	0.238
GGT (U/L)	−0.087	0.191
FPG (mmol/L)	0.135	0.042
Volume of urine (mL)	0.078	0.238
UCE (mg/24h)	−0.144	0.03
SUA (umol/L)	−0.493	<0.001
Cr (μmol/L)	0.235	<0.001
eGFR (mL/min/1.73m ²)	−0.349	<0.001

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; UUAE, 24 h urinary excretion of uric acid; FEUA, fractional excretion of uric acid; UCE, urine creatinine excretion.

Table 7 Association Between FEUA and T2D

	p	OR (95% CI)
Model 1	0.002	1.428 (1.134–1.799)
Model 2	0.040	1.310 (1.012–1.696)
Model 3	0.015	1.512 (1.083–2.111)

Notes: Model 1: Crude model; Model 2: Model 1 +adjust for age, duration, gender and BMI; Model 3: Model 2+adjust for TG/TC/LDL/HDL/SUA/Cr/ volume of urine/ glomerular hyperfiltration (GH)/ hypertension.

Discussion

According to the newest research, 34.8% of individuals were classified as overweight, while 14.1% were classified as obese in China.³⁰ Meanwhile, MetS, T2D, HUA, and hypertension³¹ are common complications of obesity. Growing clinical evidence underscores high SUA levels were a potential predictor for a wide range of metabolic disorders, including T2D,¹⁴ obesity,³² metabolic syndrome,¹⁹ and obesity-related fatty liver.³³ Since HUA is more strongly linked to cardiovascular problems¹⁷ and metabolic disorders,¹⁶ lower cut-offs for HUA have recently been established. However, studies examining the link between uric acid excretion and illnesses were lacking. This cross-sectional study was done to determine whether T2D in HUA outpatients is tied to uric acid excretion levels.

In our study, FEUA was linked to obesity and T2D. Furthermore, as opposed to the non-obesity group, UUAE was higher and FEUA was lower in the obesity group. This study's prevalence of UA underexcretion, which was 73.2%, was considerably

lower than the rate of 85% reported in the previous study.³⁴ It may be due to the different severity of HUA or gout in various individuals. Meanwhile, 13.4% of outpatients with HUA were diagnosed with T2D in our study. A meta-analysis encompassed 38 studies, the prevalence of diabetes was observed to be 19.10% in HUA.³⁵ The observed variation may be attributed to the differences in the selected populations and the smaller number of samples included in our study.

One credible hypothesis posits that insulin resistance serves as a shared pathophysiological underpinning for both diabetes and HUA.³⁶ Adipocytokines or inflammatory mediators may be formed more easily as a result of uric acid, which is believed to reduce the bioactivity of nitric oxide (NO), thereby impacting glucose uptake under insulin stimulation.¹⁴ The development and progression of HUA may be driven by hyperinsulinemia following the onset of IR because it transforms the expression of uric acid transporters.^{25,37} To compensate for elevated blood sugar, diabetic patients often have increased renal glucose excretion. The reduction in SUA levels may help to explain how glycosuria, a given criterion where blood glucose levels rise above the limit of renal reabsorption, has an impact on uricosuric activity.^{38,39} Furthermore, a study specifically demonstrated a direct correlation between elevated urinary glucose excretion rate (UEGL) and urinary uric acid excretion rate (UEUA).⁴⁰ As a facilitative glucose transporter, the GLUT9-S transporter is well known for its considerable contribution to the uricosuric impact of glycosuria.^{41–43} Meanwhile, the production of a hyperfiltration of the glomerular system condition by glycosuria and/or osmotic diuresis may have enormous consequences.⁴⁴ The current investigation discovered that FEUA was positively connected with a higher risk of diabetes, which is consistent with earlier studies.

Another credible hypothesis posits that inflammation serves as a shared pathophysiological underpinning for both diabetes and HUA. SUA is an inflammatory marker as well and it is a metabolic indicator. Type 2 diabetes mellitus is an inflammatory condition.⁴⁵ Elevated uric acid has been correlated with glycated hemoglobin.⁴⁶ Uric acid and uric acid-based markers were also related to diabetes-related disorders such as hypertension,⁴⁷ hepatic steatosis,⁴⁸ metabolic syndrome,⁴⁹ prediabetes,⁵⁰ and diabetic kidney disease⁵¹ and even new-onset diabetes.⁵² Thus, inflammation could be the common pathway between SUA and diabetes.

One potential factor contributing to HUA in patients with T2D could be a reduced urinary excretion of uric acid (UA), which may result from the compromised impact of insulin.⁵³ Indicators of insulin resistance are closely correlated with blood uric acid levels.³⁹ Furthermore, it is suggested that insulin will increase the reabsorption of uric acid, accompanied by an elevated sodium (Na^+) reabsorption within the proximal tubule.⁵⁴ If insulin is deficient, It may result in a reduction in uric acid reabsorption, which might be the reason why T2D individuals produce more uric acid than usual.

There is a suggestion that insulin resistance could serve as a mediator in the relationship between obesity and HUA. This is because adipocytes are known to potentially exacerbate insulin expression, and insulin itself has been recognized as a contributor to HUA by impeding the excretion of uric acid. Obesity might lead to an augmentation of catabolism within adipose tissue.⁵⁵ In response to a substantial purine influx, insulin resistance intensifies the reabsorption of uric acid (UA) in Otsuka-Long-Evans-Tokushima Fatty (OLETF) rats, as evidenced by the up-regulation of URAT1 expression. Simultaneously, insulin resistance diminishes UA excretion in these animals.⁵⁶

At present, there is no uniform boundary for glomerular hyperfiltration (GH) at home and abroad, and a meta-analysis of the GH threshold in 2015, which included 405 studies, showed that different researchers used different thresholds, the 75th–95th percentile above the population was typically chosen to define GH, with a threshold range of 90.7–175 mL/min/1.73 m².⁵⁷ In our study, greater than the upper quartile of EGFR, that is, $\text{EGFR} > 112 \text{ mL/min/1.73 m}^2$, was defined as GH, and that's close to the GH threshold of 118 milliliters per minute, or 1.73 m², set in a large 2018 study by the Mayo Clinic and Cleveland Clinic.⁵⁸

The exact cause of the high filtration rate in diabetes is unknown. Structural alterations brought on by increased glomerular hemodynamics, vascular activity, and metabolic factors—including mesangial dilation and thickening of the glomerular basement membrane—may be to blame.⁵⁹ Although it is known that diabetes increases uric acid excretion in the urine through voiding effects, it is unknown whether high filtration also raises the uric acid excretion fraction (FEUA). To rule out any impact that renal hyperfiltration may have on patients with diabetes' excretion of uric acid, we grouped patients to explore whether renal hyperfiltration rate affects uric acid excretion, interestingly, the high-filtration group had a lower FEUA which was in contrast to the greater FEUA in diabetic patients. On the contrary, a study that included 238 nondiabetic adolescents and 75 adolescents with type 1 diabetes(T1D) showed that FEUA was larger in

teenagers with T1D and ultrafiltration compared to counterparts without hyperfiltration.⁶⁰ The difference in conclusion may be attributed to the type of diabetes, the choice of race, and the duration of the disease. In conclusion, our results indicate that the rise in uric acid excretion in diabetes individuals may not be caused by a rise in renal filtration rate.

Limitations and Future Perspectives

Our study does have certain drawbacks, though. First of all, because this study was cross-sectional, it was unable to establish a link between disease and the amount of uric acid excretion. Secondly, given that the study participants exclusively consisted of individuals with HUA, the findings may not be generalizable to broader populations, thereby lacking in representativeness. Thirdly, numerous variables, such as dietary practices, pharmaceutical use, and genetic predispositions, affected the levels of UUA. The study's sample size is quite limited. Large-scale multidisciplinary prospective studies will be required in the future to confirm the link between metabolic illnesses and uric acid excretion.

Conclusion

Increased FEUA Levels Were Significantly Associated with T2D in HUA Patients. And there is a negative correlation between FEUA and BMI, and a positive correlation between UUA and BMI. Therefore, routine calculating of FEUA is essential for proper diagnosis and appropriate treatment of diabetes in HUA patients. A future longitudinal study with a larger sample size is needed to explore this association further.

Data Sharing Statement

The data set generated and analyzed during the current study is available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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