Fructose-associated elevation of serum uric acid levels may be involved in metabolic disorders in polycystic ovary syndrome: A case-control study

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Abstract

Objective To investigate the relationship between serum fructose and uric acid levels in patients with polycystic ovary syndrome (PCOS). Design A case-control study. Setting University-affiliated in vitro fertilization clinic. Population 292 patients with PCOS and 482 controls. Main Outcome Measures Serum fructose, uric acid and metabolic measurements. Results Compared with controls, serum fructose and uric acid levels were significantly increased in women with PCOS and patients with PCOS accompanied by metabolic disorders exhibited higher serum fructose and uric acid levels ($P < 0.001$). Restricted cubic splines indicated that serum uric acid levels linearly and positively correlated with serum fructose levels in women with PCOS ($P_{overall} < 0.001$, $P_{non\text{-}linear} = 0.30$), whereas no correlation was found in controls ($P_{overall} = 0.712$, $P_{non\text{-}linear} = 0.43$). Additionally, even after adjusting for confounding factors, serum fructose levels were an independent risk factor for hyperuricemia in patients with PCOS ($P = 0.001$; odds ratio, 1.380; 95% confidence interval, 1.207–1.577). Conclusions There was a significantly positive association of elevated uric acid levels with serum fructose levels in PCOS and was closely correlated with PCOS-related metabolic disorders, highlighting the importance of further research into the biological mechanisms of fructose and uric acid in the development of PCOS. Funding National Natural Science Foundation of China (No. 82071607 and 32100691); LiaoNing Revitalization Talents Program (No. XLYC1907071); Fok Ying Tung Education Foundation (No. 151039); Key Research and Development Program of Liaoning Province (No. 2018225062); Outstanding Scientific Fund of Shengjing Hospital (No. 202003). Keywords Fructose; Uric acid; PCOS; Metabolic disorder

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Running Title : Fructose and Uric acid in PCOS

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Tweetable abstract Elevated serum uric acid levels in PCOS are positively correlated with serum fructose levels, particularly in PCOS patients with metabolic disorders. These observations suggest a link between elevated serum uric acid and fructose metabolic dysfunction in PCOS and fructose-associated elevation of uric acid may play a key role in PCOS-related metabolic disorders.

Introduction

Polycystic ovary syndrome (PCOS) is a common and complex endocrine-metabolic disorder affecting 5-20% women of reproductive age worldwide.[1] Patients with PCOS are at an increased risk of diverse reproductive and metabolic dysfunctions, such as obesity, insulin resistance, dyslipidemia, and metabolic syndrome.[2] Using RNA sequencing techniques, our previous studies first revealed that monosaccharide biosynthesis is a novel marker for identifying patients with PCOS.[3]

Fructose is an important monosaccharide and fructose consumption is associated with the risk of developing dyslipidemia, fatty liver and insulin resistance,[4] all of which are associated with PCOS. Recently, we first found that fructose metabolism of PCOS patients has significant differences from normal controls, and the abnormal fructose metabolism may be related to obese and insulin resistance in PCOS patients.[5] Noteworthy, fructose is the only carbohydrate that generates uric acid during its metabolism[6] and a synergistic effect of fructose on uric acid levels has been suggested.[7] Fructose appears to mediate the metabolic disorders in part by raising uric acid[8] and accumulating evidence indicates that fructose-induced hyperuricemia has a key role in the development of insulin resistance.[7] Meanwhile, the importance of uric acid in reproductive diseases has been increasingly recognized, for example, serum uric acid levels are associated with increased odds of anovulation among young women.[9] Despite these advances in knowledge, the relationship between serum fructose and uric acid in PCOS remains poorly understood and their relationship with PCOS-related metabolic disorders needs to be further explored. Thus, in this study, we measure and evaluate serum fructose and uric acid levels in a same cohort from PCOS patients and control subjects, and apply a flexible and powerful approach, restricted cubic splines, to analyze the association between fructose and uric acid in women with PCOS.

Methods

Ethical approval

This study was conducted in accordance with the ethical standards and the principles of the Declaration of Helsinki. It was approved by the Institutional Review Board of China Medical University. Informed consent was obtained from all participants prior to their recruitment for the study.

Patients and sample collection

This study randomly recruited 482 participants considered as controls and 292 women with PCOS from the Center for Reproductive Medicine at the Shengjing Hospital of China Medical University between May and October 2020. PCOS was diagnosed based on the new guidelines for the diagnosis and treatment of PCOS,[10] which specify that two of the following three conditions should be satisfied: menstrual disturbance (oligomenorrhea, amenorrhea, or anovulation), clinical or biochemical signs of hyperandrogenism, and polycystic ovarian manifestations after exclusion of other etiologies. The control group consisted of healthy women and those with clinical infertility due to the involvement of the fallopian tube.

The exclusion criteria were in accordance with our previous publications.[11] These involved excluding participants with less than 3 years of menarche; smokers; pregnant women; breastfeeding women; and those having hyperprolactinemia or any other disease such as thyroid disease, diabetes, adrenal disease, or a history of any known neoplastic, infectious, or inflammatory diseases. During the 6 months prior to enrollment, none of the participants consumed drugs that would affect reproductive or metabolic functions. The characteristics of the study participants are listed in Table 1.

The basic information of the participants, including age and body mass index (BMI), was recorded using the electronic health care record databases of Shengjing Hospital, China Medical University. BMI was calculated as body weight in kilograms divided by body height in meters squared.[12] Venous blood samples were collected from the participants after 10 hours fasting between days 3 and 5 of spontaneous menstruation or progesterone withdrawal bleeding. The blood samples were centrifuged and divided into the following two parts: one part was used as the basal blood sample for testing various biochemical indicators at the laboratory of Shengjing Hospital, including the levels of serum uric acid, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone (TT), progesterone, prolactin, thyroid-stimulating hormone (TSH), fasting plasma glucose (FPG), fasting serum insulin (FSI), and lipids; the other part was stored at -80 ℃ for further determination of serum fructose, free testosterone, and dehydroepiandrosterone sulfate (DHEAS) levels. Freezing and thawing was avoided for all the samples.

Measurement of serum fructose and uric acid levels

Prior to measuring serum fructose concentrations using a fructose fluorometric assay kit (K611-100; Bio-

Vision Inc., Milpitas, CA, USA), the serum samples were diluted 1:5 in the assay buffer. The assay was performed in accordance with the manufacturer's instructions. Glucose interference was removed using a sample purification reagent. Free fructose was enzymatically processed, and the metabolites formed were reacted with the probe to generate fluorescence, which could be measured at Ex/Em 535/587 nm. The intra- and inter-assay coefficients of variation (CVs) were 7.8% and 10.2%, respectively.

Serum uric acid levels were determined using an enzymatic assay performed on an ARCHITECT ci16200 Automatic Biochemical Analyzer (Abbott Laboratories, IL, USA) using the Architect urid acid Reagent Kit (Abbott Laboratories), according to the manufacturer's and supplier's instructions. The reference range for serum uric acid levels at the study center was considered as 155-357 μmol/l, which established 357 μmol/l as a clinical diagnostic cutoff for hyperuricemia in healthy Chinese participants. The participants' characteristics are provided in Table 2.

Measurement of free testosterone and DHEAS levels

Free testosterone (CSB-E05096h, Cusabio Biotech, Wuhan, China) and DHEAS (CSB-E05105h, Cusabio Biotech, Wuhan, China) serum concentrations were measured using commercial enzyme-linked immunosorbent assay kits according to the manufacturers' protocols. The manufacturer-specified assay sensitivity limits for the detection of free testosterone and DHEAS were 3.75 pg/ml and 10 ng/ml, respectively. The concentrations were determined by comparing the optical densities (450 nm) of the samples with the standard curve. The free testosterone and DHEAS intra-assay CVs were 6.8% and 5.5%, respectively; and the inter-assay CVs values were 10.2% and 8.3%, respectively.

Subgroups of participants

To assess the levels of fructose and uric acid in various metabolic states and the impact of clinical characteristics on cases and controls, the study population was further subdivided according to PCOS-related metabolic alterations, including obesity, insulin resistance, dyslipidemia, metabolic syndrome.

According to the WHO-defined diagnostic criteria for lean, overweight, and obese individuals in Asia,[13] we categorized the participants into the following three subgroups: lean (BMI $<$ 23 kg/m^2), overweight (23 kg/m^2 [?] BMI $<$ 25 kg/m^2), and obese (BMI [?] 25 kg/m^2) (Table S1).

The degree of insulin resistance was estimated using a homeostasis model (HOMA-IR). We calculated the HOMA-IR index as follows: FPG (mM) $\times$ FSI (mIU/l)/22.5; insulin resistance could be defined as HOMA-IR $>$ 2.5; this threshold value has been widely used earlier (Table S2).[14]

Participants were classified as dyslipidemia and normolipidemia groups based on the following criteria: TC [?] 6.2 mmol/l; TG [?] 2.3 mmol/l; LDL-C [?] 4.1 mmol/l; and HDL-C $<$ 1.0 mmol/l, fulfilling at least one of the above criteria (Table S3).[15]

According to the criteria proposed by the American Association of Clinical Endocrinologists/American College of Endocrinology, the manifestation of three or more of the following factors is sufficient for the diagnosis of metabolic syndrome[16]:BMI [?] 25 kg/m^2; TG [?] 1.70 mmol/l; HDL-C $<$ 1.29 mmol/l; blood pressure [?] 130/85 mmHg; plasma glucose after a 2-h load $>$ 7.8 mmol/l, 6.1 mmol/l [?] FPG [?] 7. 0 mmol/l; other risk factors included type 2 diabetes, PCOS, sedentary lifestyle, old age, family history of hypertension or cardiovascular disease, and ethnicity with a high risk of type 2 diabetes or cardiovascular disease (Table S4).

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 24 (IBM Corp., Armonk, NY). According to the Kolmogorov-Smirnov test, continuous variables were divided into normally and non-normally distributed variables. Normally distributed continuous variables were reported as mean +- standard deviation, whereas non-normally distributed continuous variables were reported as median (quartile spacing). Differences between the PCOS and control groups were examined using an independent sample t-test (normally distributed variables) or the Mann-Whitney U test (non-normally distributed variables). One-way analysis of variance (ANOVA) with Tukey's or Dunnett's post-hoc test (two-sided) was conducted

for multi-group comparisons. Logistic regression analysis was used to determine the odds ratios (OR) with 95% confidence intervals (CI) for various characteristics associated with hyperuricemia in PCOS. All tests were two-sided, and statistical significance was defined as $P< 0.05$.

Restricted cubic splines (RCS) were conducted using R software (version 4.0.2, using packages "segmented," "splines," "Hmisc," "rms," and "ggplot2") to assess the relationship between serum uric acid and fructose levels in PCOS. We prespecified three knots located at the 10th, 50th, and 90th percentiles of serum uric acid, as recommended by Stone and Koo.[17] The RCS is a smoothly joined sum of polynomial functions, which can avoid inappropriate linearity assumptions.[18] The advantages of RCS include its ability to relate to the natural shape of the relationship and the detected sensitivity of nonlinear relationships.[19, 20]

Results

Serum fructose and uric acid levels are simultaneously elevated in women with PCOS than those in the control women

Serum fructose and uric acid levels were markedly higher in women with PCOS than those in the controls ($P < 0.001$; Table 1). To assess the impact of metabolic characteristics on cases and controls, we compared the serum fructose and uric acid levels in participants with several PCOS-related metabolic disorders (Table S1-4).

In lean, overweight and obese subgroups, serum fructose and uric acid levels were higher in women with PCOS than those in the corresponding controls ($P < 0.001$), and these levels tended to increase with an increase in BMI (Table S1). Second, serum fructose and uric acid levels were higher in patient with PCOS, irrespective of insulin resistance. Moreover, serum fructose and uric acid levels were significantly higher in the insulin-resistant group, regardless of the PCOS status (Table S2). Third, in both the dyslipidemia and normolipidemia subgroups, serum fructose and uric acid levels were higher in women with PCOS than those in the corresponding controls (Table S3). Finally, independent of the presence of metabolic syndrome, serum fructose and uric acid levels were higher in women with PCOS than those in control women, and PCOS women with metabolic syndrome presented with higher serum fructose and uric acid levels (Table S4).

In summary, serum fructose and uric acid levels were simultaneously elevated in women with PCOS than those in control women, regardless of their metabolic status. Moreover, patients with PCOS-related metabolic disorders exhibited higher fructose and uric acid levels.

Higher uric acid levels positively correlated with fructose in the overall pattern of PCOS

As stated, elevated serum uric acid levels were accompanied with increased fructose levels in women with PCOS. Therefore, using RCS models, we further explore the relationship between serum fructose and uric acid levels (Figure 1a; Supplementary Figure 1). Remarkably, there was a linear correlation between uric acid and fructose levels in women with PCOS ($P_{\text{overall}} < 0.001, P_{\text{non-linear}} = 0.30$; Figure 1a), whereas no correlation between serum uric acid and fructose levels in controls ($P_{\text{overall}} = 0.712, P_{\text{non-linear}} = 0.43$; Figure 1a).

Since there is no clear cut-off value for serum fructose levels in clinical practice, we divided women with PCOS according to the quartile of serum fructose levels. The serum uric acid levels were substantially higher combined with increasing quartiles of serum fructose levels and multivariate ANOVA confirmed differences in serum uric acid levels at different fructose levels ($P < 0.001$; Figure 1b).

Considering that clinical, biochemical, and endocrine characteristics may change with age,[21] we further stratified women with PCOS by age ($<$ 25, 25-29, 30-34, and [?] 35 years). Interestingly, there was no linear or non-linear correlation between serum uric acid and fructose levels when age was less than 25 years. In contrast, there was a non-linear association between serum uric acid and fructose levels in women with PCOS between 25 and 29 years of age ($P_{\text{overall}} = 0.001$, $P_{\text{non-linear}} = 0.\ 01$). After 30 years of age, there was a significant linear correlation between serum uric acid and fructose levels in women with PCOS (Figure 1c).

PCOS-related metabolic alterations exhibit positive associations between uric acid and fructose

As described previously, both serum fructose and uric acid levels were strongly associated with PCOS-related metabolic alterations, we used RCS to detect a possible dependency of serum levels of uric acid and fructose in PCOS with diverse metabolic disorders.

Serum uric acid levels were markedly and positively associated with serum fructose levels in PCOS in all metabolic disorders; however, no such correlation was observed in the corresponding control participants (Figure 2). In the obese PCOS subgroup, there was a non-linear correlation between serum uric acid and fructose levels in PCOS ($P_{\text{overall}} < 0.001$,$P_{\text{non-linear}} = 0.02$; Figure 2b). Additionally, serum uric acid levels linearly associated with fructose levels in PCOS with insulin resistance, dyslipidemia and metabolic syndrome (Figure 2d, f, h).

These results suggested that the correlation between elevated serum uric acid and fructose levels in PCOS could be attributed to PCOS itself and was independent of the metabolic disorders in the population.

Serum fructose levels are independently associated with hyperuricemia in PCOS

As shown in Table 2, the prevalence of hyperuricemia in the PCOS group was 42.12%, which was significantly higher than that in the control group (12.03%). Specifically, among all the groups, PCOS women with hyperuricemia had the highest serum fructose levels, and there was no difference in serum fructose levels between the hyperuricemia and non-hyperuricemia subgroups of control women ($P > 0.05$).

Then, we evaluated the clinical factors contributing to the risk of hyperuricemia in women with PCOS (Table 3). After adjusting for confounding factors affecting hyperuricemia via univariate logistic regression analysis, including age, BMI, HOMA-IR, free testosterone, HDL-C, and triglycerides, elevated serum fructose levels were strongly associated with a high risk of hyperuricemia in PCOS ($P = 0.001$; OR, 1.380; 95% CI, 1.207–1.577; Table 3).

Discussion

In this study, we reported for the first time that elevated serum uric acid in women with PCOS strongly and positively correlated to serum fructose, and serum fructose is an independent risk factor for hyperuricemia in women with PCOS. In addition, PCOS patients with metabolic dysfunction are usually found to have higher serum fructose and uric acid levels and there is a strong and positive association between elevated uric acid levels and fructose levels. These observations first suggested a link between elevated serum uric acid and fructose metabolic dysfunction in PCOS and fructose-associated elevation of uric acid may play a key role in PCOS-related metabolic disorders.

As reviewed by Taskinen et al., fructose influences several metabolic pathways which result in the generation of uric acid.[22] In the liver, fructose is primarily phosphorylated to fructose 1-phosphate, significantly decreasing intracellular phosphate and adenosine triphosphate levels. This decrease stimulates adenosine monophosphate deaminase (AMPD), which catalyzes the degradation of AMP to inosine monophosphate, producing uric acid.[23] Fructose also stimulates uric acid synthesis from amino acid precursors[24] and competes with uric acid for renal excretion, reducing the rate of uric acid excretion and increasing blood uric acid levels.[25] Although these studies have provided preliminary insights into the mechanism of fructose metabolism to produce uric acid, to date, no study has investigated the relationship between elevated fructose and uric acid in PCOS. Our studies have first confirmed the close and positive association between elevated serum uric acid and fructose levels in PCOS. Elevated serum uric acid levels may reflect an underlying disorder of fructose metabolism in patients with PCOS that further emphasize the potential and critical clinical role of measuring serum uric acid levels in routine practice.

In recent years, the treatment of PCOS not only aims at its hyperandrogenemia and infertility symptoms, but also focuses on its metabolic disorders. An interesting finding of this study is that PCOS patients with metabolic disorders showed higher serum fructose and uric acid levels, with a strong positive correlation. Previous studies provided evidence to support our results. High-fructose is associated with several PCOS-

associated metabolic disorders, including dyslipidemia, insulin resistance, weight gain, and cardiovascular effects.[26] Uric acid is a product of fructose metabolism and involved in reproductive and endocrine metabolic disorders.[27] Mounting evidence has shown that uric acid promotes the development of insulin resistance, lipid metabolism disorders, and metabolic syndrome.[28] Notably, fructose metabolism can induce hyperuricemia reduces NO levels in endothelial cells and induces insulin resistance.[29] Moreover, uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome.[30] Collectively, the potential role of fructose-associated elevation of serum uric acid in PCOS may be its effects on the metabolic disorders of PCOS. These preliminary results open new avenues toward improving our understanding of the biological role of fructose and uric acid in the metabolic disorder of PCOS.

The major strength of this study is that this is the first study to evaluate the relationship between serum uric acid and fructose levels in PCOS. Another strength of this study is the application of RCS, a flexible and powerful approach, to analyze the linear/non-linear relationship between fructose and uric acid in participants with different metabolic statuses. We further confirmed that elevated serum uric acid levels were positively correlated with serum fructose levels in PCOS with metabolic disorders, whereas no correlation was found in the controls. Additionally, our study still had several limitations. Although various biochemical measurements associated with PCOS have been considered, other possible covariates (such as diet, smoking, and ethnicity) were not evaluated and the mechanisms underlying the elevated fructose and uric acid levels in women with PCOS remain unclear which need to be clarified in follow-up research.

Conclusion

In summary, this study first found the there was a significantly positive association of elevated uric acid levels with serum fructose levels in PCOS and was closely correlated with PCOS-related metabolic disorders, suggesting elevated serum uric acid levels may reflect an underlying disorder of fructose metabolism in PCOS and highlighting the importance of further research into the biological mechanisms of fructose and uric acid in the development of PCOS.

Disclosure of interests

The authors declare no conflict of interest.

Contribution to authorship

DL, BS and DF conceived and designed the study. DL, BS, DF, JS, PL, HJ, YM, HY and YP performed data acquisition and interpretation. DL, BS, DF, JS, and PL wrote the paper. DL, BS, and DF have accessed and verified the data. All authors confirmed that they had full access to all the data in the study and accepted responsibility to submit for publication.

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Legends for Figures and Tables

Figure 1. Association between serum uric acid and fructose levels in the overall pattern.

a, Association between serum uric acid and fructose in control women and women with PCOS, allowing for nonlinear effects, with 95% CI. b, Differences in serum uric acid levels with varying fructose levels among women with PCOS. c, Age-stratified association between serum uric acid and fructose levels in women with PCOS. *P* values were adjusted for multiple comparison. CI, confidence interval; PCOS, polycystic ovary syndrome.

Figure 2. RCS models of the association between serum uric acid and fructose levels.

Association between serum uric acid and fructose levels using RCS analysis in participants with (a-b) obesity, (c-d) insulin resistance, (e-f) dyslipidemia, and (g-h) metabolic syndrome. CI, confidence interval; IR, insulin resistance; Mets, metabolic syndrome; PCOS, polycystic ovary syndrome; RCS, restricted cubic splines.

Table 1 . Description of the study participants.

Table 2 . Description of the study participants according to the presence or absence of hyperuricemia.

Table 3 . Univariate and multivariate logistic regression analyses evaluating the factors affecting hyperuricemia in PCOS.

Supporting Information

Figure S1. Association between serum uric acid levels and variables in women with PCOS in restricted cubic spline models, allowing for nonlinear, with 95% CI. CI, confidence interval.

Table S1. Description of the study participants according to BMI.

Table S2. Description of the study participants according to HOMA-IR.

Table S3. Description of the study participants according to the presence or absence of dyslipidemia.

Table S4. Description of the study participants according to the presence or absence of metabolic syndrome.

Table 1. Description of the study participants.

	Control	PCOS	p-value
N	482	292	
Age (years)	32.00 (30.00-35.00)	30.00 (27.00-32.00)	0.001
BMI (kg/m^2)	22.50 (20.40-25.00)	26.20 (23.3-29.4)	0.001
Φρυστοσε (μM)	**8.53 (7.43-9.61)**	**9.64 (8.56-11.50)**	**0.001**

	Control	PCOS	p-value
Υρις αςιδ (μM)	**280.40 (243.18-328.00)**	**343.35 (292.40-397.08)**	**0.001**
FSI (mIU/L)	10.00 (7.30-13.90)	13.50 (9.60-19.50)	0.001
FPG (mM)	5.20 (4.94-5.52)	5.31 (5.03-5.65)	0.005
HOMA-IR	2.33 (1.63-3.21)	3.24 (2.28-4.60)	0.001
TT (μg/L)	0.46 (0.34-0.60)	0.65 (0.50-0.83)	0.001
FT (pM)	21.28 (16.34-28.25)	29.12 (21.59-38.31)	0.001
DHEAS (μM)	2.78 (1.91-3.89)	3.96 (2.77-5.83)	0.001
AMH (pM)	20.25 (9.70-32.80)	60.68 (37.43-87.50)	0.001
FSH (IU/L)	7.24 (6.16-8.73)	6.16 (5.24-7.51)	0.001
LH (IU/L)	4.07 (2.92-5.47)	8.50 (5.22-12.83)	0.001
Estradiol (ng/L)	46.00 (35.00-66)	52.00 (40.00-73.00)	0.001
P (μg/L)	0.59 (0.39-0.81)	0.61 (0.41-0.89)	0.291
Prolactin (μg/L)	11.20 (8.79-14.84)	10.17 (7.82-14.28)	0.002
TSH (mIU/L)	1.84 (1.40-2.59)	1.80 (1.31-2.48)	0.305
TC (mM)	4.52 (4.00-5.04)	4.76 (4.28-5.42)	0.001
LDL-C (mM)	2.67 (2.21-3.16)	2.98 (2.54-3.56)	0.001
HDL-C (mM)	1.32 (1.11-1.54)	1.15 (0.97-1.36)	0.001
Triglycerides (mM)	0.92 (0.65-1.30)	1.35 (0.94-1.95)	0.001

Abbreviations: AMH, anti-mullerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FSI, fasting serum insulin; FT, free testosterone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; P, progesterone; PCOS, polycystic ovary syndrome; TC, total cholesterol; TSH, thyroid-stimulating hormone; TT, total testosterone; Mean ± standard deviation or median (interquartile range) are shown. The Mann-Whitney U test was used for non-normal distribution data and the Student's t -test was used for normal distribution data.

Table 2 . Description of the study participants according to the presence or absence of hyperuricemia.

	Control			PCOS	
	Non-HUA	**HUA**	P-value	**Non-HUA**	**HU**
Hyperuricemia [n (%)]	424 (87.97%)	58 (12.03%)		169 (57.88%)	123
Age (years)	32.00 (30.00-35.00)	31.00 (29.00-35.00)	0.176	30.00 (28.00-33.00)	29.
BMI (kg/m^2)	22.00 (20.20-24.50)	25.10 (22.87-27.91)	0.001	24.97 (21.95-28.5)	27.
Φρυςτοσε (μM)	**8.53 (7.41-9.59)**	**8.53 (7.85-9.67)**	**0.539**	**9.02 (8.05-10.73)**	**11**
Υρις αςιδ (μM)	**272.30 (237.90-307.68)**	**389.20 (371.48-408.15)**	**0.001**	**302.00 (269.70-327.30)**	**40**
FSI (mIU/L)	9.80 (7.20-13.10)	13.10 (10.25-19.08)	0.001	11.90 (8.70-15.65)	16.
FPG (mM)	5.18 (4.93-5.50)	5.37 (5.09-5.78)	0.003	5.19 (4.96-5.58)	5.3
HOMA-IR	2.26 (1.59-3.05)	3.17 (2.37-4.67)	0.001	2.80 (1.97-3.71)	3.9
TT (μg/L)	0.47 ± 0.19	0.48 ± 0.19	0.848	0.67 (0.50-0.80)	0.6
Free testosterone (pM)	21.90 (15.64-27.92)	24.52 (19.00-31.00)	0.011	28.45 (20.92-36.33)	29.
DHEAS (μM)	2.73 (1.88-3.84)	3.17 (2.09-4.34)	0.040	3.65 (2.71-5.42)	4.3
AMH (pM)	19.57 (9.25-32.36)	23.93 (16.73-36.59)	0.018	62.21 (38.50-88.96)	57.
FSH (IU/L)	7.40 (6.21-8.81)	6.62 (6.00-7.69)	0.001	6.28 (5.24-7.60)	5.9
LH (IU/L)	4.17 (2.94-5.59)	3.63 (2.62-4.95)	0.135	8.70 (5.10-13.75)	8.3
Estradiol (ng/L)	47.00 (36.00-68.00)	40.00 (30.00-53.00)	0.004	52.00 (40.00-75.00)	53.
P (μg/L)	0.60 (0.40-0.84)	0.49 (0.35-0.71)	0.009	0.64 (0.45-1.01)	0.5
Prolactin (μg/L)	11.35 (8.90-14.99)	10.88 (8.16-13.33)	0.230	10.45 (8.03-14.72)	9.8

	Control			PCOS	
TSH (mIU/L)	1.85 (1.38-2.60)	1.83 (1.51-3.02)	0.366	1.79 (1.29-2.37)	1.9
TC (mM)	4.50 (3.99-5.04)	4.57 (4.12-5.08)	0.392	4.69 (4.25-5.30)	4.8
LDL-C (mM)	2.68 ± 0.70	2.85 ± 0.62	0.076	2.93 (2.52-3.45)	3.0
HDL-C (mM)	1.35 (1.15-1.59)	1.08 (0.94-1.30)	0.001	1.20 (1.05-1.46)	1.0
Triglycerides (mM)	0.89 (0.64-1.18)	1.44 (1.05-2.31)	0.001	1.21 (0.84-1.79)	1.6

Abbreviations: AMH, anti-mullerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FSI, fasting serum insulin; FT, free testosterone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HUA, hyperuricemia; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; P, progesterone; PCOS, polycystic ovary syndrome; TC, total cholesterol; TSH, thyroid-stimulating hormone; TT, total testosterone; Mean ± standard deviation or median (interquartile range) are shown. The Mann-Whitney U test was used for non-normal distribution data and the Student's t -test was used for normal distribution data.

Table 3. Univariate and multivariate logistic regression analyses evaluating the factors affecting hyperuricemia in PCOS.

	Univariate regression	Univariate regression	Univariate regression	Multivariate regression	Mult
Factor	OR	95% CI	P-value	OR	95%
Age (years)	0.920	0.862-0.982	0.012*	0.924	0.858
BMI (kg/m^2)	1.113	1.055-1.174	0.001*	1.008	0.944
Φρυςτοσε (μM)	**1.404**	**1.239-1.592**	**0.001***	**1.380**	**1.20**
FSI (mIU/L)	1.088	1.052-1.125	0.001*		
FPG (mM)	1.850	1.151-2.975	0.011*		
HOMA-IR	1.392	1.223-1.584	0.001*	1.256	1.082
TT (μg/L)	0.831	0.482-1.434	0.506		
FT (pM)	1.018	1.003-1.034	0.018*	1.008	0.993
DHEAS (μM)	1.000	1.000-1.000	0.571		
AMH (pM)	0.985	0.941-1.031	0.513		
FSH (IU/L)	0.966	0.859-1.085	0.555		
LH (IU/L)	0.966	0.927-1.006	0.091		
Estradiol (ng/L)	0.997	0.991-1.002	0.254		
P (μg/L)	0.931	0.806-1.075	0.329		
Prolactin (μg/L)	0.964	0.922-1.007	0.098		
TSH (mIU/L)	1.201	0.964-1.497	0.102		
TC (mM)	1.213	0.923-1.594	0.167		
LDL-C (mM)	1.310	0.972-1.765	0.077		
HDL-C (mM)	0.148	0.062-0.353	0.001*	0.281	0.099
Triglycerides (mM)	1.336	1.066-1.676	0.012*	1.069	0.840

Abbreviations: AMH, anti-mullerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FSI, fasting serum insulin; FT, free testosterone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; P, progesterone; PCOS, polycystic ovary syndrome; TC, total cholesterol; TSH, thyroid-stimulating hormone; TT, total testosterone, *P<0.05.

Figure 1

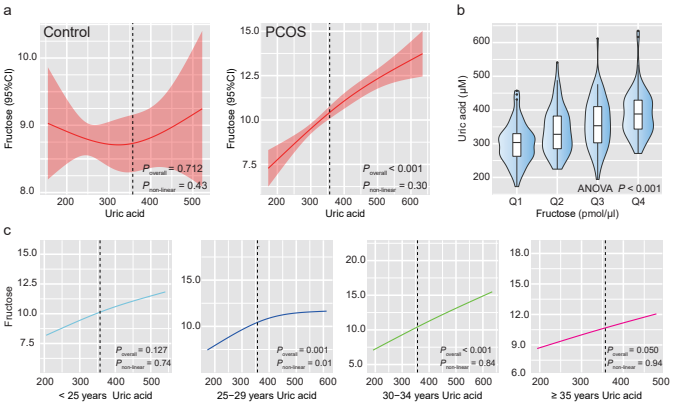
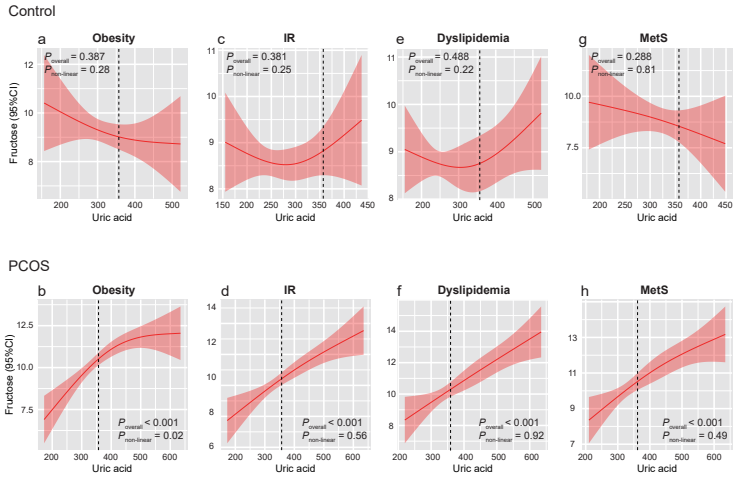


Figure 2



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