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Uric Acid Relationship with Noninsulin-Based Insulin Resistance Indices in Selected Metabolic Disorders: A Systematic Critical Review

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ABSTRACT

OBJECTIVES: Uric acid (UA) has a role in pathogenesis of several metabolic abnormalities including insulin resistance (IR) and their related disorders. The aim of this report is to review the available evidences that reveal the association between UA, IR and related disorders via both noninsulin and insulin-based IR indices.

METHODS: The published literature was surveyed using Google Scholar and PubMed entering the terms Obesity, UA, IR, Metabolic Syndrome (MetS), Gestational Diabetes (GDM), Polycystic Ovarian Syndrome (PCOS).

RESULTS: UA had substantial positive relationships with IR, as well as obesity, MetS, DM, GDM, and PCOS. Evidently UA with a role in oxidative stress, endothelial dysfunction and induction of inflammation may cause IR in totality, the major factor in development of MetS and related diseases. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), insulin based IR index, correlated positively with UA. Moreover, specifically triglyceride to high density lipoprotein cholesterol ratio (TG/HDL-C), visceral adiposity index (VAI), lipid accumulation product (LAP), triglyceride to fasting glucose (TyG) index are noninsulin-based IR indices of positive correlations with UA. MetS score for IR (MetS-IR), a non-insulin based IR index, had significantly proportional correlations with MetS components as well as UA level. UA to HDL-cholesterol ratio (UHR) was a pronounced statistical predictor of MetS and diabetes control. UA positively associated with hyperinsulinemia and IR in prediabetes.

CONCLUSION: Succinctly UA can be an emerging biochemistry marker of predictive role in IR, MetS and related anomalies. More hyperuricemia related studies are warranted to be oriented from being correlational to mechanistic.

Keywords: Uric acid, insulin resistance, nascent Metabolic Syndrome, Gestational Diabetes, Polycystic Ovarian Syndrome (PCOS).

INTRODUCTION

Uric acid (UA) is an end product of metabolic catabolism of purine nucleotides (adenine and guanine) and the apprehensive causative agent of severe, acute and chronic inflammatory arthritis, gout. It has the role of antioxidant in liver, vascular endothelial cells and in the nasal sectretions[1]. UA has a relationship with several diseases and conditions such as diabetes mellitus (DM), nascent metabolic syndrome (MetS), polycystic ovarian syndrome (PCOS), and obesity through different pathological mechanisms. Many studies were conducted to verify these correlations.

Pathophysiological Mechanisms of UA

UA has different roles in inflammation and coronary endothelial dysfunction. Inflammatory markers such as high-sensitivity-C-reactive protein (hsCRP) and neutrophil count as well as increased homeostatic model

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assessment of insulin resistance (HOMA-IR) and so the risk of T2DM positively correlated with high serum UA level.[2a] Several pathological mechanisms were proposed for the role of UA in different diseases and conditions. Predominantly UA may induce inflammation through other several pathways including its pivotal role in Toll-like receptors (TLR)/NOD like receptor P3 (NLRP3) dependent activation and release of IL-1β and IL-18.[2b] First of all, UA irreversibly inhibits the production of nitric oxide (NO) leading to oxidative stress and endothelial dysfunction in different body tissues. This inhibition may lower insulin sensitivity and increase insulin level in skeletal muscles. It may induce proinflammatory markers in adipose tissues; this mechanism may increase the risk of hypertension, insulin resistance (IR) and MetS.[3] UA may change the lining of vascular system, exposing it to thrombosis and inflammation and so may increase the risk of cardiovascular diseases (CVD) such as DM and hypertension (HTN).[4] High level of UA may increase the production of reactive oxygen species (ROS) which may result in inflammation via augmenting the expression of inflammatory markers and in low insulin secretion and sensitivity.[5]. Another supposed mechanism of UA is increasing the activity of platelets and therefore thrombotic risk of many conditions such as arrhythmia, heart failure (HF), DM, MetS, and chronic kidney disease (CKD).[6] Markedly asymptomatic hyperuricemia was more likely a consequence of body mass index (BMI) in metabolically unhealthy obesity, unlike metabolically healthy obesity and metabolically unhealthy and healthy non-obesity.[7a] In displaying effectively the role of gut microbiota diversity and abundance in hyperuricemia; the antibiotic-fed high-purine-induced hyperuricemia rats had *significantly lower* UA content compared to the hyperuricemia-only rats, and gut microbiota (fecal microbiota transplant; FMT) from hyperuricemia rats increased UA content of recipient rats. The genera *Vallitalea, Christensenella* and *Insolitispirillum* may associate with hyperuricemia.[7b] Further Abnormal metabolism of gut microbiota reveals the possible molecular mechanism of nephropathy induced by hyperuricemia.[7c] In addition; as IR can be linkage between hyperuricemia of gouty arthritis and dyslipidemia.[8a] UA has a positive correlation with cholesterol production, and so on the risk of MetS; it modifies the homeostasis of cholesterol by increasing its endogenous synthesis. It is proportionally correlated with surrogate markers of cholesterol synthesis represented by ratio of lathosterol to total cholesterol and the ratio of lathosterol to compesterol index which represents the ratio of biosynthesis to intestinal absorption of cholesterol. In addition, it was found that UA has a positive correlation with triacylglycerol (TAG), low density lipoprotein-cholesterol (LDL-C), and negative correlation with high density lipoprotein-cholesterol (HDL-C).[8b]

UA correlations with Metabolic Abnormalities

UA and noninsulin based- as well as insulin-based Insulin Resistance (IR)

Insulin Resistance (IR) is a characteristic of several clinical conditions such as obesity, DM, and cardiovascular diseases. The major mechanism of IR is the low grade systemic inflammation. Inherent immunity and infection are supposed mechanisms of IR pathogenesis.[9] Several studies reported a correlation between UA and IR. A study which was conducted on non-diabetic patients showed that UA level was positively associated with IR using TyG index as a measure of IR.[10] High UA was correlated positively for HOMA-IR as a measure of IR in females but not in males.[11] IR is associated with autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). IR was measured in these patients by using TyG index, and it was found to be correlated positively with high UA level.[12] Another study conducted on patients with different levels of glucose tolerance to measure IR.

Four surrogate markers were used in the study and showed positive correlation with UA level. These markers include triglyceride to high density lipoprotein cholesterol

ratio (TG/HDL-C), visceral adiposity index (VAI), LAP, triglyceride to fasting glucose (TyG) index.[13] Opposite results were found in a cross sectional study which was conducted on non-diabetics with different levels of BMI. UA was found to be increased with increasing BMI. HOMA-IR as a marker of IR was found to be higher in overweight and obese, but no significant association was found between UA and IR. It is ambiguous weather high UA level is a result or a cause of IR, so UA cannot be used as alternative marker of IR.[14a] Conversely BMI, hyperinsulinemia, and insulin resistance (HOMA-IS) were independent risk factors of hyperuricemia in obese subjects. [14b]

UA and nascent Metabolic Syndrome (MetS)

MetS is a cluster of interrelated metabolic risk factors that increase the risk of cardiovascular morbidity and mortality.[15] It occurs simultaneously in the same individual, and results from systemic alterations in several organs and tissues; it includes abdominal obesity, dyslipidemia, hypertension, and hyperglycemia.[16-17] Many surrogate markers are used to predict MetS by measuring insulin resistance (IR). In a cross sectional study, triglyceride-waist circumference (TG-WC) and lipid accumulation product (LAP) were the most potent markers of IR that predict MetS.[18] Another cross sectional study reported that triglyceride-glucose index (TyG index) as a measure of IR is the most powerful marker for diagnosing of MetS compared to other IR indices such as fasting glucose, triglycerides, and HOMA-IR.[19] MetS score for IR (MetS-IR) is an indirect measure of non-insulin based IR which correlates fasting glucose with fasting triglycerides, BMI, and HDL-C. It has positive correlations with MetS components and it may be used to predict T2DM.[20] The same index was found in another study to have a positive relationship with hypertension as a component of MetS in patients who have normal BMI.[21] Most significantly the TG/HDLc, TyG, and METS-IR all had positive correlations with UA level in subjects without self- reported use of antihyperuricemic agents, hypoglycemic agents, or lipid-lowering drugs.[22] UA has correlations with MetS and its criteria. A cross sectional study which was the first study conducted on American children and adolescents to identify the prevalence rate of MetS at different concentrations of UA. The study showed increased prevalence of MetS with increased serum concentration of UA.[23] Higher UA level was reported in obese children compared to controls, the same study showed a correlation between UA concentration and MetS criteria.[24] In Liu et al. study (2010), the risk of MetS and its criteria increased with high serum concentration of UA in both men and women. The same study reported a significant positive correlation between central obesity and high UA in women but not statistically significant correlation in men.[25] In the study by Zhu et al. (2017), high serum level of UA associated with metabolic abnormalities such as high blood pressure, blood sugar, and lipid profile, as well as BMI.[26] Another cross sectional study was conducted on obese and non-obese diabetic inpatients. A positive association was found between high serum UA and obesity markers such as BMI and waist to hip ratio (WHR) in diabetic patients.[27] In a retrospective study that used for the first time UA to HDL-cholesterol ratio (UHR) as a predictor of MetS and diabetes control, UHR was found to be lower in well controlled diabetes compared to poorly controlled ones, as well as it was lower in diabetic patients without MetS compared to diabetic with MetS.[28] UA levels significantly correlated with 2-hour insulin levels and HOMA-IR scores in the prediabetes of impaired glucose regulation group.[29a] Obviously, that increasing the number of MetS components is associated with increasing level of UA. Pronouncedly favipiravir, as a proposed COVID19 treatment, can adversely increase serum UA in MetS patients. This can be exacerbated by combination therapy as MetS can be a risk factor of COVID19 progression and prognosis. [29b]

UA and Diabetes mellitus

DM has become a prevalent problem around the world. Many factors and mechanisms may involve in the development of DM. IR is a main pathological mechanism which contributes in the incidence of DM as well as other metabolic disorders.[30] The relation between UA and DM has become a hot topic of research, but controversy still exists. Some studies showed that high level of UA increase the risk

of development of DM. The study which was conducted on diabetic, non-diabetic, and prediabetic patients reported that patients who had impaired glucose tolerance (IGT) and DM had greater level of UA compared to normoglycemic ones.[31] In a cross sectional observational study conducted on diabetic and non-diabetic persons, higher serum UA concentration was noticed among diabetic and prediabetic compared to controls.[32] Another large cohort study was conducted on normoglycemic and prediabetic patients aged over 45 years. The study showed a positive association between UA level and the incidence of prediabetes (preDM) in normoglycemic ones, but no significant increase in incidence of DM among preDM patients. This may be due to the correlation of UA to the early phase mechanisms of DM.[33]

In a population based study, healthy persons were followed up for development of DM. The persons who had high serum UA were at more risk of development of DM.[34] several studies were conducted to correlate UA level with blood glucose level and HbA1c, as in Deb et al. study (2019) which was conducted on healthy persons and diabetic patients who had different level of blood glucose and HbA1c. The study demonstrated higher level of UA among diabetic participants compared to controls. In addition, the study reported that increasing level of blood glucose and HbA1c was associated with increasing level of UA.[35] Similar findings were found in a Saudi study, in which diabetic patients had higher level of UA compared to healthy ones, and HbA1c positively but not significantly correlated with UA level in diabetic patients.[36] Inverse findings were found in a cross sectional study conducted on US adults. A negative correlation between UA level and DM was reported. The proposed mechanism for this finding is the inhibition of UA reabsorption by high blood glucose level.[37] UA had been found to increase the risk of complications associated with DM such as albuminuria and renal damage.[38-39a] Interestingly intestinal microbiota of gout (mainly *Bacteroides caccae* and *Bacteroides xylanisolvens*) are enriched, thus are more similar to those of T2D than to liver cirrhosis. This may be related to disorders of purine degradation and butyric acid biosynthesis in gout patients. [39b] Substantially T2D patients infected with SARS-CoV-2 had decreased levels of BMI, lymphocytes, UA, and albumin, and increased CRP levels.[39] Evidently COVID-19 patients had UA and UA/Creatinine values lower than normal at admission. Male COVID-19 patients with low UA levels had a significantly higher risk of developing severe symptoms than those with high UA levels. During the aggravation course of the disease, the level of UA gradually decreased until discharge. At follow-up exam, the level of UA is similar to the levels at admission.[39c]

In terms of gestational diabetes mellitus (GDM), several studies demonstrated a positive correlation between high UA level in first trimester and the risk of developing GDM as in Laughon et al. study (2009).[40] Similar findings were found in El-Gharib et al. study (2013).[41] A case control study on pregnant women with and without GDM reported higher UA level among GDM women compared to controls.[42] In a retrospective study on registered births, the level of UA in the first period of pregnancy positively correlated with GDM.[43] In another study, 300 first trimester pregnant women were screened for serum UA, and followed till term. The study reported amazing correlation between UA level in the first trimester and the incidence of GDM.[44a] Substantially UA in patients of pregnancy hyperglycemia was much higher than those of healthy pregnant women. In the third trimester, COVID-19 infection in pregnant patients raised high risks of ketonuria, hypercoagulable state, and hyperfibrinolysis, which may lead to severe complications. COVID-19 increased the inflammatory responses of placenta, and fetuses and neonates had potential organ dysregulation and coagulation disorders. There was a potential intrauterine transmission while pregnant women had high titer of SARS-CoV-2, but it is necessary to detect SARS-CoV-2 in the blood cord, placenta, and amniotic fluid to further confirm intrauterine infection of fetuses.[44b]

UA and Obesity

Obesity is strongly correlated with IR; which may play a role in pathogenesis of obesity complications. Obesity may cause impairment and dysfunction of insulin sensitive tissues.[45] Obesity strongly associated with UA level. A cross sectional study was conducted on Thai adolescents' boys and girls showed high UA level in obese boys compared to those who had normal weight.[46] Similar findings were reported between UA level and obesity in Japanese children.[47] Another cross sectional study on obese and non-obese Bangladeshi adults showed significant positive correlation between UA level, obesity and its markers such as body mass index (BMI), waist circumference (WC), and hip circumference (HC). Higher UA level among overweight and obesity group compared to underweight group.[48] In a cohort study, it is found that UA had a correlation with all-cause mortality rate, but no significant correlation with cardiovascular mortality rate in obese adults.[49] On the contrary, the first study on obesity and its correlation with UA reported positive but weak relationship between high UA and obesity due to co presence of other factors affecting the obesity.[50a] Importantly in the general population, gout is associated with many risk factors for poor COVID-19 outcomes; it is more common in men than in women, it occurs more often in older individuals, and it is strongly associated with overweight and obesity, CVD, T2D, and chronic kidney disease. Thus even when gout patients are not prescribed immunosuppressants, their comorbidities mean that they have among the highest risk of poor COVID-19-related outcomes of all patients with rheumatic diseases.[50b]

UA and Poly Cystic Ovarian Syndrome (PCOS)

PCOS is an endocrinologic disease occurs in premenopausal women. Several studies have reported that patients with PCOS may suffer from deterioration of insulin secretion which may progress into other diseases such as DM.[51] Reproductive hormones play a role in hyperuricemia in females with PCOS. A retrospective cross sectional study was conducted on women with PCOS showed higher concentration of serum UA in those women compared to women without PCOS.[52] Another study showed a significant higher UA level in women with PCOS, this may be due to increased metabolism of UA by androgens which are present in high concentration in PCOS.[53] The same findings were found in Swetha et al. study (2013).[54] On the other hand, conflicting results were found in Leustean et al. study (2015). The study reported non-significant difference in serum UA concentration between PCOS and non PCOS groups; this may be due to small sample size. The same study demonstrated a positive relationship between sera UA, BMI, and WC as markers of obesity.[55a] Mechanistically the testosterone level was positively associated with the prevalence of hyperuricemia in females with PCOS. [55b] Visceral adiposity index (VAI) was independently associated with hyperuricemia in PCOS patients. [55c] Principally FMT were promising subordinate therapy option in altered microbiota-relevant hyperuricemia. [7b] Besides urease inhibitors are nominated treatment option in hyperuricemia induced nephropathy.[7c] Of importance, diversity and abundance of gout treatment options are widely elaborated and discussed in light of COVID19 infection. [50b].

Conclusion

UA has several correlations with different conditions and diseases. Positive association was found between UA and each of IR, DM, GDM, MetS, obesity, and PCOS. UA can be used to predict the incidence of these diseased conditions, but further causality longitudinal investigations are required to confirm that.

CONFLICT OF INTEREST the authors declare no conflict of interest.

CONTRIBUTIONS OF AUTHORS the authors equally contributed to this manuscript composition

Abbreviation Table

BMI	Body mass index
CKD	Chronic Kidney Disease
CRP	C-reactive protein
DM	Diabetes mellitus
GDM	Gestational diabetes mellitus
HC	Hip circumference
HDL-C	High density lipoprotein-cholesterol
HF	Heart failure
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hs-CRP	High-sensitivity C-reactive protein
HTN	Hypertension
IGT	Impaired glucose tolerance
IR	Insulin resistance
LAP	lipid accumulation product
LDL-C	Low density lipoprotein-cholesterol
MetS	Metabolic syndrome
NO	Nitric Oxide
PCOS	Poly cystic ovarian syndrome
preDM	Prediabetes
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
TAG	Triacylglycerol
TG/HDL-C	Triglyceride to high density lipoprotein cholesterol ratio
TyG-WC	Triglyceride-glucose index*waist circumference
UA	Uric acid
UHR	Uric acid to HDL-cholesterol ratio
VAI	Visceral adiposity index
WC	Waist circumference
WHR	Waist to hip ratio

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علاقة حمض اليوريك مع مؤشرات مقاومة الأنسولين الغير المعتمدة على الانسولين في والاضطرابات ذات الصلة بالأيض : مراجعة نقدية منهجية

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ملخص

الأهداف: يمتاز حمض اليوريك بأن له دور في التسبب في العديد من الاضطرابات الأيضية بما في ذلك مقاومة الأنسولين والاضطرابات المرتبطة بها. ان الهدف من هذا التقرير هو مراجعة الأدلة المتاحة التي تكشف عن الارتباط بين حمض اليوريك ومقاومة الانسولين والاضطرابات ذات الصلة عبر مؤشرات مقاومة الانسولين المعتمدة وغير المعتمدة على الانسولين.

الطريقة: تم مسح الأدلة المنشورة باستخدام **Google Scholar** و **PubMed** بإدخال مصطلحات السمنة، حمض اليوريك، مقاومة الانسولين، متلازمة التمثيل الغذائي،سكري الحمل، ومتلازمة تكيس المبايض.

النتائج: أظهر حمض اليوريك علاقات إيجابية كبيرة مع مقاومة الانسولين ، بالإضافة إلى السمنة ،متلازمة الأيض الغذائي، مرض السكري،سكري الحمل، ومتلازمة تكيس المبايض. من الواضح أن حمض اليوريك له دور في الإجهاد التأكسدي ، والخلل البطاني وتحريض الالتهاب الذي قد يسبب مقاومة الانسولين والتي تعد العامل الرئيسي في تطور متلازمة الأيض الغذائي والأمراض ذات الصلة. نموذج تقييم مقاومة الأنسولين المتجانس والمعتمد على الانسولين أظهر ارتباطا إيجابيا مع حمض اليوريك.علاوة على ذلك و على وجه التحديد ، نسبة الدهون الثلاثية إلى نسبة كوليسترول البروتين الدهني عالي الكثافة ،مؤشر السمنة الحشوية ، منتج تراكم الدهون ، مؤشر الدهون الثلاثية إلى جلوكوز الصائم والتي هي مؤشرات مقاومة انسولين غير معتمدة عليه أظهرت ارتباطات إيجابية مع حمض اليوريك.كما أظهرت نسبة متلازمة الأيض الغذائي الى مقاومة الانسولين ، والتي هي مؤشر مقاومة انسولين غير معتمد على الانسولين ارتباطات متناسبة بشكل كبير مع مكونات متلازمة الأيض الغذائي وكذلك مستوى حمض اليوريك.وقد كانت نسبة حمض اليوريك إلى نسبة كوليسترول البروتين الدهني عالي الكثافة مؤشراً إحصائياً واضحاً للتنبؤ بمتلازمة الأيض الغذائي ومرض السكري.كما أظهرحمض اليوريك ارتباطا إيجابيا بفرط انسولين الدم ومقاومة الانسولين في مرض ماقبل السكري.

الخلاصة: يمكن أن يكون حمض اليوريك بإيجاز علامة كيميائية حيوية ناشئة للتنبؤ بحدوث مقاومة الانسولين ومتلازمة الأيض الغذائي والاضطرابات ذات الصلة. هناك ما يبرر توجيه المزيد من الدراسات المتعلقة بفرط حمض يوريك الدم من كونها مترابطة إلى آلية

الكلمات الدالة: حمض اليوريك ، مقاومة الأنسولين ، متلازمة التمثيل الغذائي ، سكري الحمل ، متلازمة تكيس المبايض.

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