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Assessment of the Correlation between Hyperuricemia and Insulin Resistance in hyperuricemic patients at Al-Khums Diabetic Center (KDC)

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Abstract:
Insulin resistance (IR) is a crucial factor in the development of type 2 diabetes mellitus (T2DM), and its association with hyperuricemia remains an area of ongoing investigation. This study aimed to assess the correlation between hyperuricemia and IR in individuals attending the Al-Khums Diabetic Center (KDC). A prospective study included 80 volunteers from the KDC, with fasting blood samples drawn for uric acid (UA), fasting blood sugar (FBS), glycated hemoglobin (Hb1Ac), insulin levels, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Hyperuricemic participants received a daily allopurinol dose (100 mg) for two months, and subsequent blood samples were collected to analyze the effects on insulin levels and impaired glucose tolerance. The results showed that hyperuricemic patients exhibited significantly elevated FBS levels (108.44 mg/dl ± 19) compared to the control group (85 mg/dl ±22). Moreover, Hb1Ac, insulin levels, and HOMA-IR increased notably, reaching (5.381%± 0.477%), (23.951 IU/L ±17), and (6.5±6.7), respectively, in comparison to the control group's (4.9%±0.59), (8.395 IU/L ±6.499), and (1.77±1.52), with a statistically significant p-value < 0.05. Our findings also revealed that hyperuricemic patients treated with Allopurinol (100 mg) for two months experienced a reduction in FBG, Hb1Ac, insulin levels, and HOMA-IR, measuring (95.87 mg/dl ±8.3), (5.32%±0.20), (10.68 IU/L ±2.93), and (2.54±0.81), respectively. This contrasts with pre-allopurinol hyperuricemic individuals whose measurements were (113.33 mg/dl ± 16), (5.66%± 0. 35), (28.9 IU/L ±9.6), and (7.86±3.07) respectively, demonstrating a significant difference with a p-value < 0.05. In conclusion, the study suggests a higher prevalence of IR in hyperuricemic patients, with additional findings indicating that allopurinol improves insulin sensitivity, potentially preventing T2DM.

Keywords: Hyperuricemia, Allopurinol, Insulin Resistance, T2DM.

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تقييم العلاقة بين فرط حمض البوليك ومقاومة الانسولين لدى مرضى فرط حمض البوليك في مركز الخمس لأمراض السكري

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الملخص
مقاومة الأنسولين هي عامل رئيسي يؤدي للإصابة بمرض السكري من النوع 2، وعلاقته بارتفاع حمض اليوريك لازالت قيد البحث، هدفت هذه الدراسة إلى تقييم العلاقة بين فرط حمض البوليك ومقاومة الأنسولين لدى المترددين على مركز مكافحة وعلاج مرض السكري بالخمس حيث اشتملت الدراسة على 80 متطوعًا من المترددين على مركز مكافحة وعلاج مرض السكري بالخمس، حيث تم سحب عينات الدم لتقييم حمض البوليك*(UA)* ، وسكر الدم الصائم*(FBS)* ، والهيموجلوبين السكري*(Hb1Ac)* ، ومستوى الأنسولين، ونموذج التوازن لمقاومة الأنسولين *(HOMA-IR)*. تلقى المشاركون الذين يعانون من ارتفاع حمض البوليك جرعة يومية من دواء الالوبيورينول (100 ملغ) لمدة شهرين، وتم جمع عينات الدم بعد تناول العلاج لدراسة تأثيره على مستويات السكر والأنسولين في الدم، وأظهرت النتائج ارتفاع في مستويات السكري لدى المرضى الذين يعانون من فرط حمض البوليك قدره (108.44± 19) ملغ/دل، مقارنةً بـ (85±22) ملغ/دل للمجموعة الضابطة. وبالإضافة إلى ذلك، كان هناك زيادة ملحوظة في الهيموجلوبين السكري ومستويات الأنسولين ونموذج التوازن لمقاومة الأنسولين *(HOMA-IR)* حيث بلغت (5.381 ±0.477%)، (17±23.951)، و (6.7±6.5) على التوالي، مقارنة بالمجموعة الضابطة التي كانت (0.59±4.9)، (6.499±8.395)، و (1.52±1.77) على التوالي، مع قيمة إحصائية معنوية أقل من 0.05 ، كما بينت النتائج أن المرضى الذين يعانون من فرط حمض البوليك والذين تم علاجهم بالالوبيورينول (100 ملغ) لمدة شهرين شهدوا انخفاضًا في سكري الدم و الهيموجلوبين السكري ومستويات الأنسولين ونموذج التوازن لمقاومة الأنسولين *(HOMA-IR)* ، بقيم (8.3±95.87)، (0.20±5.32)، (2.93±10.68)، و (0.81±2.54) على التوالي. وهذا القيم تختلف عن النتائج قبل تناول دواء الالوبيورينول التي كانت (113.33 ± 16)، (5.66± 0. 35)، (9.6±28.9)، و (3.07±7.86) على التوالي، مما يظهر فارقًا معنويا أقل من 0.05، ختاما تشير هذه الدراسة إلى أن مقاومة الأنسولين كانت أكثر شيوعًا لدى المرضى الذين يعانون من فرط حمض البوليك كما أن علاج فرط حمض اليوريك يحسن من مقاومة الأنسولين، مما يؤدي إلى منع الاصابة بالسكري من النوع 2.

الكلمات المفتاحية: فرط حمض البوليك، الالوبيورينول، مقاومة الأنسولين، السكري من النوع 2.

Introduction

UA is the final oxidation product of purine metabolism generated during enzymatic degradation of hypoxanthine and xanthine, [1] produced by the liver and excreted by the kidneys, with recognized antioxidant action when its blood levels are within physiological limits. However, the increase in its serum levels is called hyperuricemia.[2]

Hyperuricemia is arbitrarily defined as a serum UA concentration above 7.0 mg/dl in men and 6.0 mg/dl in women. Hyperuricemia may occur from excessive urate production (overproduction) or decreased elimination (under excretion), and frequently a combination of both processes occurs in the same patient. Hyperuricemia, the precursor of gout, is strongly associated with IR syndrome, an established risk factor for T2DM, cardiovascular disease, and also plays a role in developing renal and metabolic diseases in diabetic patients. [1] Moreover, recent prospective studies with representative samples indicate hyperuricemia as a predictor for developing IR and T2DM. [2]

IR is a common metabolic disease in which insulin activity in target tissues is impeded. It is typically characterized as the ineffective control of glucose metabolism by a given circulating concentration of insulin. Because insulin serves multiple functions in humans, compensatory hyperinsulinemia caused by an inability to control glucose metabolism usually has negative physiological consequences in other organs and systems. [3]

Metabolic syndrome is a grouping of physiological and anthropometric nutrient metabolism abnormalities such as hyperglycemia, hyperuricemia, and hyperlipidemia. The metabolism of three

primary nutrients is inextricably intertwined. Hyperuricemia may contribute to improper glucose metabolism, IR, and potentially pancreatic β-cell death. [4]

Some ideas for the metabolism of uric acid-induced gluconeogenesis have been proposed [5]; for example, it found that UA increased hepatic gluconeogenesis by inhibiting adenosine monophosphate kinase, which regulates the rate-limiting enzymes cytoplasmic phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, both of which are involved in gluconeogenesis in the liver. This finding implies that urate-lowering treatment may diminish gluconeogenesis in gout patients with metabolic syndrome. Although T2DM is a comorbid condition of gout, pathological activation of anti-interleukin (IL)-1β plays a role in both gout and T2DM. [6,7] Additionally, Canakinumab (an IL-1β monoclonal antibody) relieves pain and inflammation and reduces the risk of new pain flares in patients with acute gouty arthritis.[8] Moreover, the genetic risk factors and the incidence rate of gout and type 2 diabetes are interdependent. [9] Prospective data from two generations of the Framingham Heart Study have revealed that individuals, including young adults with higher serum UA, are at a higher risk of T2DM. [10]

Two observational studies in the United Kingdom and the United States (white people) have shown that gout is associated with an increased risk of type 2 diabetes [11,12], and that T2DM, paradoxically, is associated with an inverse risk of gout in the Caucasian population in the United Kingdom. [13,14] According to a Taiwanese National Health Insurance (NHI) claims data-based study, the incidence of T2DM among gout patients was higher than that of gout in T2DM patients.[9]

Lowering UA levels has also been reported to improve IR in animal models of metabolic syndrome. [15,16] Although interventional studies in humans are limited, lowering UA has been reported to improve IR in subjects with congestive heart failure. [17] And HbA1c levels in normotensive diabetic subjects.[18]

Small-scale research studies have shown that allopurinol (300 mg/day) improves GC, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR), in patients with asymptomatic hyperuricemia across 3-month therapy periods. [19]

Given this background data, we designed a prospective randomized study to determine if lowering UA with allopurinol therapy (a xanthine oxidase inhibitor prescribed for gout or asymptomatic hyperuricemia) can improve fasting glucose levels and IR in nondiabetic subjects with asymptomatic hyperuricemia. [20

Material and methods

This prospective study was conducted on 80 volunteers who attended the KDC from April to the end of September 2022. investigated the correlation between hyperuricemia and IR. Patient histories were collected through interviews and a standardized questionnaire covering personal details and medical history. Participants were grouped into three categories: Group-I (Control) involved 25 non-hyperuricemic participants, Group-II (Hyperuricemic patients) involved 55 participants diagnosed as Hyperuricemic patients and Group-IIIa, including 15 volunteers from Group-II receiving Anti-hyperuricemic medication (Allopurinol 100 mg). Anti-hyperuricemic medication was administered based on medical guidelines, and study investigations were conducted two months post-treatment. Fasting blood samples collected from (Group-IIIb) post two months of treatment facilitated a comparative analysis before and after anti-hyperuricemic administration.

Results

The study was conducted on 55 blood samples from hyperuricemic patients and 25 non-hyperuricemic individuals. The total number of precipitants was 80 individuals; 42.5% were males, and 57.5% were females; the mean age was 45 years, and the age range was (20–65 y) attending the outpatient clinic of Al-Khums Diabetes Center (KDC).

Table (1) compares hyperuricemic group II with control group I, including the FBG, HbA1C, Insulin, and HOMA-IR,

The hyperuricemic patient's group II showed a significant increase in FBG, the mean (108.44± 19) when compared to the control group I (85±22) ($p<0.05$). In addition, group II showed a significant increase in HbA1C (5.381% ± 0.477) when compared to group I (4.9% ±0.59) ($p<0.05$).

The group II demonstrated a significant increase ($p<0.05$) in insulin level, the mean (23.951±17), when compared to the group I (8.395±6.499). Also, there was a significant difference in HOMA IR (<0.05) between group II and group I, which illustrates that IR was more frequent in group II than group I.

Table 1 Comparison between of hyperuricemic group II and the control group I.

Parameter	Hypouricemic group II (No.55) mean±SD	Control group I (No.25) mean±SD	P. value
Uric Acid (mg/dl)	7.603±1.15	3.78±1.09	0.000
FBG (mg/dl)	108.44± 19	85±22	0. 021
HbA1C (%)	5.381± 0.477	4.9±0.59	0. 024
Insulin level (IU/L)	23.951±17	8.395±6.499	0. 001
HOMA IR	6.5±6.7	1.77±1.52	0. 004

Table 2 shows the effect of the administration of Allopurinol (100 mg) on 15 hyperuricemic patients (group III) for two months. Regarding the relationship between hyperuricemia and IR, 15 cases of the hyperuricemic group IIIa who agreed to continue participating were referred to an internist to prescribe anti-hyperuricemia medication (allopurinol) according to the medical guidelines. After two months of treatment, subsequent blood samples were collected from group IIIb to analyze the effects on insulin levels and impaired glucose tolerance.

Table 2 Effects of Allopurinol administration on hyperuricemic patients after two months of treatment.

Parameter	group IIIa Before allopurinol administration (No.15) mean±SD	group IIIb Post two months of allopurinol administration (No.15) mean±SD	p. value
Uric Acid (mg/dl)	8.07±1.17	6.47±0.40	0.000
FBG (mg/dl)	113.33± 16	95.87±8.3	0.000
HbA1C (%)	5.66± 0. 35	5.32±0.20	0.000
Insulin level(IU/ml)	28.9±9.6	10.68±2.93	0.000
HOMA IR	7.86±3.07	2.54±0. 81	0.000

The current study found that the mean serum UA in group IIIa was (8.07±1.17). In contrast, the Serum UA concentrations in group IIIb were significantly decreased (6.47±0.40) ($p<0.05$).

The study indicated that the mean FBS level measured before allopurinol administration among hyperuricemic patients (group IIIa) was (113.33± 16). At the same time, the hyperuricemic patients post two months of allopurinol administration (group IIIb) revealed a significant reduction in serum glucose level (95.87±8.3) ($p<0.05$). In addition, (group IIIb) revealed a significant reduction of Hb1Ac ($p<0.05$).

Group IIIb, demonstrated a significant decrease in insulin levels and HOMA-IR, the mean (10.68±2.93) and (2.54±0.81), respectively. Compared to hyperuricemic patients (group IIIa) before allopurinol administration (28.9±9.6) and (7.86±3.07), respectively ($p<0.05$).

Discussion

The findings of our study align with several previous investigations that have examined the relationship between hyperuricemia and IR. observed similar patterns in increased insulin levels and IR indices among hyperuricemic individuals. The consistent elevation in HbA1C in both studies suggests a potential synergy between hyperuricemia and metabolic dysregulation. [21]

In agreement with our results, a meta-analysis conducted by Chen et al. reported a positive correlation between hyperuricemia and elevated fasting blood glucose levels. Our study's observed increase in FBG among hyperuricemic patients supports the hypothesis that hyperuricemia may contribute to impaired glucose metabolism. [22]

A study by Dehghan et al. involving a large cohort demonstrated that elevated serum UA is an independent risk factor for IR and type 2 DM. The consistent elevation in IR parameters, including HOMA-IR and Insulin, supports the notion that hyperuricemia might contribute to the pathogenesis of insulin resistance, corroborating our results. [23]

Moreover, the association between hyperuricemia and altered glucose metabolism was investigated in animal models. A study by Kanbay et al. conducted on rats showed that inducing hyperuricemia led to IR and impaired

glucose tolerance. This preclinical evidence supports our clinical findings of increased FBG and HbA1C levels in hyperuricemic patients. [24]

Our study extends the existing literature by investigating the therapeutic effects of Allopurinol on hyperuricemia-associated IR. This aligns with a randomized controlled trial by Zhang et al., which demonstrated that Allopurinol intervention improved insulin sensitivity and glucose metabolism in hyperuricemic individuals. The study findings demonstrate that the administration of allopurinol resulted in a simultaneous decrease in both HOMA-IR and insulin levels, so providing further support for the possible effectiveness of this medication. [25]

The administered Allopurinol in our study exhibited promising results, aligning with research by Goicoechea et al., which demonstrated that Allopurinol treatment improved insulin sensitivity in patients with hyperuricemia. The reduction in UA levels, along with improvements in HOMA-IR, Insulin, and glucose parameters post-allopurinol, suggests a potential treatment approach to target IR that is related to hyperuricemia. [26]

A study by Krishnan et al. found no significant association between serum UA levels and IR in a community-based sample. [27]

Our study contributes to the growing evidence indicating a substantial association between hyperuricemia and IR. The observed increases in HOMA-IR, Insulin, FBG, and HbA1C in hyperuricemic patients align with the findings of several studies.

Conclusion

Our results suggest that hyperuricemia is associated with an increased risk of T2DM, probably due to IR or hyperinsulinemia as part of a cluster of metabolic abnormalities connected to T2DM. The additional data demonstrate that lowering UA by antihyperuricemic medication (Allopurinol) enhances IR and FBS, all of which protect against the development of T2DM.
Future study is needed to evaluate whether allopurinol improves not just glucose homeostasis but also micro- and macrovascular problems in T2DM patients.

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