

TYPE 2 DIABETES MELLITUS PATIENTS WITH AND WITHOUT HYPERTENSION: XANTHINE OXIDASE ACTIVITY AND URIC ACID CONCENTRATION

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Abstract: A metabolic condition known as type 2 diabetes mellitus (T2DM) has spread all over the world. Pancreatic insulin resistance and β -cell dysfunction are its defining features. In 2021, almost 537 million people worldwide had diabetes. The prevalence of hypertension (HTN) in T2DM more than 50% result from uncontrolled blood glucose. The prevalence of microvascular and macrovascular complications in T2DM with HTN, more common than in those without HTN. Hyperglycemia is related to overproduction of reactive oxygen species (ROS) and oxidative stress (OS). The etiology of metabolic disorders is associated with OS. On the other hand, OS increases the risk of cardiovascular disease (CVD) by causing endothelial dysfunction. An important source of ROS is xanthine oxidase (XOD), while uric acid (UA) has two properties: pro- oxidant and antioxidant. Sixty T2DM patients with and without hypertension participated in this research. These patients were compared to a control group of thirty people. Lipid profile, XOD and UA were determined in this research. The results of the study showed a significant increase in XOD and UA values in T2DM patients compared to controls. The elevated OS agents and lipids biomarkers mainly in T2DM group could contribute to increasing cardiometabolic risks and weakening the overall health status of the participants. Triglyceride (TG), total cholesterol (TC), LDL-c and HDL-c abnormalities are risk factors of CVD. Dyslipidemia and elevated HbA1c in diabetic patients can be considered as a very high-risk group for CVD.

Keyword: Oxidative stress, Hyperglycemia, Hypertension, Cardiovascular diseases.

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Introduction

A metabolic disease, known as type 2 diabetes mellitus (T2DM) has spread worldwide.¹ It is characterized by insulin resistance leading to β -cell dysfunction.² In 2021, about 537 million people were suffering from T2DM. The number may increase to 783 in 2045, depending on the statistics of the International Diabetes Federation.³ Many complications of T2DM, such as hypertension (HTN), result from uncontrolled blood glucose.⁴ Increased blood glucose leads to deposition of advanced glycation of end product on the arterial wall and generation of reactive oxygen species (ROS), which causes damage to the arterial.⁵ One effect of prolonged exposure of the vascular wall to elevated glucose level is reduced arterial flexibility. Reduced flexibility causes increased peripheral vascular resistance, which causes HTN.⁶ Furthermore, more than fifty percent of T2DM patients have HTN.⁷ Microvascular and macrovascular problems are substantially more possible in people with T2DM and HTN than they are in people without HTN.⁸ T2DM patients with HTN are the most common CVD-related cause of morbidity and mortality, at a rate of 80%.⁹ Additionally, HTN hastens the development of CVD, diabetic renal disease, and diabetic cardiomyopathy. According to a study on T2DM patients, having HTN increases the risk of death and cardiovascular events by 44% and 41%, respectively, compared to 7% and 9% for those who only have diabetes.¹⁰ When oxidants outnumber antioxidants in a ratio favoring oxidants, it is known as oxidative stress (OS). OS leads to molecular damage by impairment redox signaling and control, and it is correlated with a variety of diseases, such as infections, neurodegenerative diseases and CVD.¹¹ Cells

create ROS to control cellular activities in both physiological and pathological states.¹² In β -cells, glucose metabolism is essential for the production of insulin. A highly activated glucose metabolism results in the production of ROS, which reduces the efficiency of insulin secretion.¹³ According to numerous studies on T2DM, the levels of OS are significantly and abnormally increased.¹⁴ The endothelium is a crucial component of cardiovascular physiology because it creates an interface between the blood and surrounding tissues and participates in the movement of nutrients and metabolites.¹⁵ Endothelial dysfunction is considerably exacerbated by hyperglycemia-induced overproduction of ROS and OS, which is linked to the pathophysiology and development of metabolic disorders.² Xanthine oxidase (XO) is a major cause of ROS¹⁶ and it generates the ROS in the cells.¹⁷ Uric acid has both antioxidant and pro-oxidant properties in vitro by scavenging and production of ROS.¹⁸

Chemicals and Methods

Patients

Sixty T2DM patients, 27 males and 33 females, participated in this study. The average of their age was 57.18 ± 8.8 years. In this research, thirty patients have hypertension. The samples were taken between September 2022 and January 2023 at Al-Najaf Hospital in Najaf Governorate of Iraq. According to the WHO diagnostic criteria, patients identified as having fasting plasma glucose levels 7.0 mmol/L and HbA1c $>6.5\%$, self-reported hypertension, current use of anti-hypertensive medication, or three or more consecutive readings of systolic blood pressure (SBP) 140 mmHg and/or diastolic blood pressure (DBP) 90 mmHg are considered to be signs of

hypertension. The study excluded kidney, liver, heart, thyroid, and CRP-positive patients who had any systemic problems that could have an impact on the parameters being examined. Individuals with these conditions were screened based on their medical histories.

Healthy group: Thirty individuals who appeared to be in good health (13 men and 17 women) were categorized as the control group. The ages resembled those of the patients being studied. CRP was negative in their groups.

Body mass index values

Obesity was defined by body mass index (BMI), which was calculated using the formula: $BMI (kg/m^2) = Weight (kg) / (Height m)^2$. The WHO categorizes adults as underweight (BMI $< 18.5 kg/m^2$), normal weight (BMI = $18.5-24.9 kg/m^2$), overweight (BMI = $25.0-30.0 kg/m^2$), and obese (BMI $> 30.0 kg/m^2$). This classification is used in the current investigation.

Biochemical studies

Blood specimens: Using plastic syringes with single-use needles, a specimen of 5 mL of venous blood was drawn from each patient or control. Two tubes were used for the samples' transfer. For the measurement of HbA1c, 2 ml of freshly obtained venous blood were taken in an EDTA tube. Three milliliters of blood were placed in a gel tube and allowed to sit at room temperature for 30 minutes to allow for clotting before being centrifuged at 3000 xg for ten minutes. The serum was then extracted and transferred into a new, disposable plain tube (hemolysis samples were discarded), where it was kept in the freezer ($-20\text{ }^{\circ}\text{C}$) until analysis.

*Instruments for experimentation***Table 1.** Instruments and apparatus for laboratories.

Instruments	Company	Origin
Centrifuge	Hettich	Germany
Deep freezer	Hitachi	Japan
ELIA Microplate reader	BioTek	USA
Glass gel tube	Q.L.lab	China
Micropipette	Dragon	China
Refrigerator	Hitachi	Japan
Spectrophotometer	Spectra721	Taiwan
Sphygmomanometer	Chi157	China
Water bath	Hettich	Germany

*Chemicals***Table 2.** Chemical compounds and study kits.

Type of Kits	Company/Country
Blood Glucose	Spinreact/Spain
CRP	LTD/Britain
HbA1c	BT LAB/ China
HDL-c	Biolabo/ France
Triglyceride	Biolabo/ France
T.cholesterol	Biolabo/ France
Uric acid	Biolabo/ France
XOD	BT LAB/ China

Analytical Statistics

Using the Kolmogorov-Smirnov test, the distribution types of the results group were examined. The two types of variable results - nonparametric and regularly distributed - are separated by a statistical distribution. For the normally distributed variable, the results were reported

as (mean \pm standard deviation). Pooled t-tests were used to compare the control, patient, and divided groups based on the parameters that were measured. When p value is 0.05, the distinction between groups is taken into statistical consideration as being different. The statistical analysis was done using SPSS Statistics base 26 and IBM-USA software. With Microsoft Office 2016, Excel was used to evaluate the data.

Results and discussion

1-Comparison between T2DM patients and Healthy group

Table 3 displays the demographic and clinical data for the T2DM and control groups.

Table 3. Participants' demographic and clinical data.

Variable	T2DM Patients (60) Mean \pm SD	Healthy group (30) Mean \pm SD	p-value
Age (year)	57.1 \pm 8.82	57.13 \pm 6.12	0.988
No of male/female	27/33	13/17	0.882
Duration disease (year)	12.01 \pm 6.54	-	-
Smoking (Yes/No)	9/51	8/22	0.222
Systolic BP	12.39 \pm 1.13	11.76 \pm 0.66	0.0024
Diastolic BP	8.05 \pm 0.57	7.7 \pm 0.50	0.0041
BMI (kg/m ²)	29.04 \pm 4.42	28.45 \pm 5.43	0.6074
FBG (mg/dl)	277.23 \pm 77.55	98.33 \pm 5.6	< 0.0001
HbA1c %	8.52 \pm 1.53	5.54 \pm 0.59	< 0.0001
Family History of diabetes (Yes/No)	32/28	0/30	-
CRP P/N	0/60	0/30	-

BP: blood pressure; **BMI:** Body mass index; **FBG:** Fasting blood glucose; **HbA1c:** Glycated hemoglobin; **p:** positive, **N:** negative.

Globally, T2DM is on the rise as a result of alterations in aging, diet, lifestyle, and diabetes care. Age and BMI do not significantly differ

between patients and controls. In T2DM compared to the healthy group, there is an expected substantial rise in FBS ($p < 0.0001$) and HbA1c. The overall health of T2DM patients is impacted by the age at which they are diagnosed with the condition. There is mounting evidence that T2DM affects β -cell function more quickly than T2DM with a later onset. Also, relevant to an elevated risk of mortality and morbidity is young-onset T2DM. HbA1c measurement is regarded as a crucial diagnostic tool for keeping track of dietary restrictions and medication regimens during the management of diabetes.¹⁹ The glycemic control is when the patients have HbA1c less than 7%.²⁰ In this study, the patients have uncontrol blood glucose, where the mean of HbA1c is approximately 8.5 %. The clinical factors that influence the glycemic control of patients included duration of T2DM,²¹ fasting glucose, postprandial glucose, time of disease diagnosis,²² HTN,²³ microangiopathy, levels of total cholesterol (TC) and low-density lipoprotein (LDL).²⁴ The rate of uncontrolled blood glucose was 1.79 times greater in people with diabetes who had the disease for more than seven years compared to those who had it for that short of time.²⁴ This supports the findings of earlier research,²⁵ which showed that the likelihood of uncontrolled blood glucose increases with the duration of diabetes. Diabetes that has been present for a longer period of time has deteriorated beta cell activity, making blood glucose control challenging.²⁶ Glycemic management is a useful strategy for lowering the cardiovascular effects of diabetes.²⁵ Hyperglycemia with hyperinsulinemia and inflammation that causes OS all play a role in vascular remodeling. This causes atherosclerosis and an increase in peripheral vascular resistance, leading to the uncontrolled BP.²⁷

*Lipid Profile***Table 4.** Lipid profile data of the participants.

Parameters	T2DM Patients (60)	Healthy group	p-value
	Mean±SD	(30) Mean±SD	
TC mg/dl	285.95±42.32	158.16±10.22	<0.0001
TG mg/dl	248.13±45.68	151.31±23.57	<0.0001
HDL-c mg/dl	45.38±6.31	40.62±4.8	0.0001
VLDL-c mg/dl	49.62±9.13	30.26±4.72	<0.0001
LDL-c mg/dl	190.75±45.02	87.23±12.37	<0.0001
TyG	10.17±0.397	8.89±0.17	<0.0001

TC: total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; VLDL-c: very low density lipoprotein cholesterol; LDL-c low density lipoprotein cholesterol and TyG: triglyceride-glucose index.

In this study, the levels of serum total cholesterol, TG, HDL-c, VLDL-c, LDL-c, and TyG index are significantly higher in T2DM patients compared to controls ($p < 0.0001$). Uncontrolled blood glucose may be associated with dyslipidemia. A Korean study found that poor glycemic control was 1.73 times more common in cases where the TC level was 200 mg/dL or higher than in cases where it was 200 mg/dL.²⁸ The primary causes of death in diabetics are high TC and uncontrolled blood sugar because atherosclerosis has increased cerebrovascular and CVD.²⁹ One study found that dyslipidemia in T2DM patients increase with age because of the workload as well as poor physical activity.³⁰ In Korea, 35% of T2DM patients have hypercholesterolemia, which raises the risk of CVD, according to the Diabetes Fact Sheet from 2018.²⁸ This supports the findings of Pyo et al., who demonstrated that elevated TC considerably worsens poor glycemic control.³¹ However, studies by Gu 2019 and Park 2016 found that cholesterol does not affect blood glucose levels.^{32,33} Due to increased insulin

resistance, increased production and secretion of LDL-c and TG in the liver, and increased fatty acid release from fat cells, dyslipidemia develops in diabetic individuals, becoming a risk factor for uncontrolled blood sugar levels.³⁴

Determination of triglyceride-glucose (TyG) index is considered as a biomarker of insulin resistance.³⁵ In 2018, as novel marker for metabolic problems, the TyG has recently been linked to an increased risk of CVD in those who appear to be in good condition.³⁶ In a Jordanian study, the most frequent lipid abnormality found in T2DM patients is with high TG/low HDL-c ratio. According to numerous studies, obesity promotes lipolysis, which results in a significant release of free fatty acids and development of hypertriglyceridemia. Along with this, the liver also produced more VLDL and TG, two substances that may help T2DM patients develop atherosclerosis and CVD.³⁷ Also, researchers have looked at how insulin inactivity caused by obesity causes an increase in lipid profiles and a major impact on HbA1c levels.³⁸

Xanthine oxidase and Uric acid

The results of oxidant parameters in T2DM patients and healthy controls are presented in figure 1.

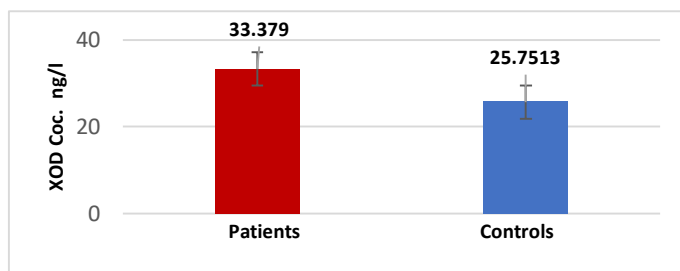


Figure 1. Serum XOD in T2DM patients and Controls in bars plot.

There is a significant increase in XOD ($p < 0.0001$) in T2DM compared with healthy group. The incidence of CVD events, heart failure,

and renal dysfunction is linked to the activation of XOD in plasma and/or tissue.³⁹ Circulating XOD can compete with sulfated glycosaminoglycans for heparin's binding sites on the surface of endothelial cells.¹⁶ This causes endothelial activation during pro-oxidant and pro-inflammatory states, which in turn causes endothelial dysfunction.⁴⁰ Hence, insufficient XOD activation can increase ROS, leading to OS-induced damage in a variety of tissues.⁴¹ According to Lassén et al., increased XOD activity is thought to be a source of both extracellular and intracellular ROS in diabetes.⁴² By XOD, hyperglycemia-induced endothelial dysfunction causes cardiovascular problems in addition to neuropathy. Drugs that reduce XOD activity have been shown to enhance cardiovascular and renal outcomes in animal models by reducing tissue damage brought on by OS.⁴³ According to research by Furuhashi et al, plasma XOD activity may be a new metabolic biomarker because it has been demonstrated to be independently linked with obesity, smoking, liver dysfunction, hyperuricemia, dyslipidemia, and insulin resistance in the general population.⁴⁴

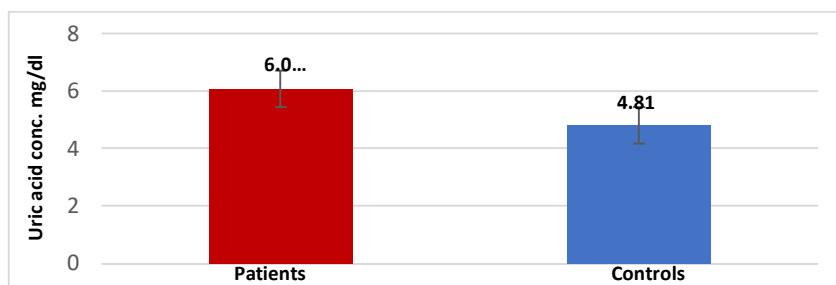


Figure 2. SUA in T2DM patients and healthy in bars plot.

There is a significant increase in serum uric acid (SUA) ($p = 0.00012$) in T2DM compared with healthy group. The development of CVD is known to be risk-factored by an increase in UA.⁴⁵ Gout risk can be increased by hyperuricemia, which also increases SUA associated with the metabolic syndrome, including glucose intolerance, abdominal obesity, dyslipidemia, and HTN.⁴⁶ According to earlier research, the relationship between increased SUA and the onset of metabolic and vascular disorders

may be mediated through insulin resistance, inflammation, and OS.⁴⁷ In addition to urolithiasis and gout, obesity and metabolic disorders like insulin resistance, dyslipidemia, and HTN are all strongly correlated with hyperuricemia. As a result, it has been proposed that a rise in UA serves as a stand-in marker of metabolic syndrome. With rising fasting insulin levels and homeostasis model assessments of insulin resistance, UA levels rise linearly. Nonetheless, there is a bell-shaped relationship between uric acid level and fasting glucose and HbA1c levels.⁴⁸

2-Comparison of T2DM with and without hypertension

The clinical and demographic data of T2DM patients with and without HTN are presented in Table 5.

Table 5. Clinical and Demographic data of T2DM with and without Hypertension patients.

Variable	Patients (30) Mean±SD	Hypertension (30) Mean±SD	p-value
Age (year)	54.1±4.46	60.11±6.44	0.0102
No. of male/female	17/13	11/19	0.181
Duration of Disease (year)	11.34±5.31	12.78±7.75	0.4115
Smoking (Yes/No)	6/24	3/27	0.338
Systolic BP mmHg	11.84±0.57	13.13±1.4	0.00012
Diastolic BP mmHg	7.75±0.51	8.57±0.96	0.00025
BMI (kg/m ²)	28.59±4.31	29.56±4.58	0.4026
FBG (mg/dl)	230.23±73.34	223.11±83.27	0.7058
HbA1c %	8.38±1.52	8.68±1.55	0.4557
Family History Yes/No	18/12	14/16	0.634
CRP Positive/Negative	0/30	0/30	-

Age, SBP, and DBP are all significantly higher in people with T2DM and HTN. The individuals with HTN in this study are elderly. This

result indicated that older age with T2DM causes complication such as hypertension. Increase in hypertension in T2DM patients may be associated with some factors including being older than 60, having diabetes for a longer period of time, being physically inactive, and being overweight or obese.⁴⁹ Other reasons for prevalence of hypertension in older people with T2DM are the combined effects of increasing insulin resistance and declining pancreatic islet function with age.⁵⁰ Age-related structural changes in the arteries, notably stiffness in the large arteries, are the main cause of blood pressure increase. High blood pressure is associated with increased cardiovascular risk.⁵¹ HTN and T2DM are complex because hyperglycemia raises extracellular fluid osmolality, and HTN in people with DM is typically thought to be volume dependent.⁵² As a result, the extracellular fluid volume increases as water moves from the intracellular space to the extracellular space (to maintain osmotic balance), leading to intracellular dehydration and a state of volume overload (unless hyperglycemia is sufficiently severe to cause osmotic diuresis, in which volume overload is less possible). Moreover, endothelial cells are crucial for preserving vascular homeostasis, and their failure is linked to metabolic diseases like CVD. Thus, it is believed that the primary cause of HTN in people with T2DM is endothelial dysfunction.⁵³ Between T2DM with and without HTN, there is a significant rise in both systolic and diastolic BP. These data make a compelling case for the possibility of a reciprocal relationship between T2DM and HT. They both contribute to the development of renal disease and/or arterial HTN. It is highly associated with the duration of diabetes.⁵⁰ Assessed BP down to 120 mmHg and 70 mmHg could reduce mortality, macrovascular, and microvascular events. Hence, decreasing BP lowers

CVD events and microvascular complications and improves CVD outcomes in both T2DM patients and non-T2DM patients.⁵⁴

Lipid profile

Comparison between HTN and T2DM Patients in Lipid profile in Table 6.

Table 6. Lipid profile data in T2DM and HTN groups.

Parameters	T2DM (30) Mean ± SD	HTN (30) Mean ± SD	p-value
TC mg/dl	283.47±43.25	297.29±25.1	0.131
TG mg/dl	249.4±54.66	246.66±33.54	0.8136
HDL-c mg/dl	50.63±7.72	42.26±7.7	0.0001
VLDL-c mg/dl	49.88±10.93	49.33±6.7	0.8136
LDL-c mg/dl	182.95±45.33	205.69±27.26	0.0207
TyG	10.19±0.41	10.14±0.38	0.688

TC: total cholesterol; **TG:** triglyceride; **HDL-c:** high density lipoprotein cholesterol; **VLDL-c:** very low density lipoprotein cholesterol; **LDL-c** low density lipoprotein cholesterol and **TyG:** triglyceride-glucose index.

In this study, TC, TG, VLDL-c, and TyG are not significantly different between the T2DM and hypertension groups. LDL-c and HDL-c levels in hypertension patients differ significantly from those without T2DM.

Patients with T2DM and HTN must take metabolic dyslipidemia into account when determining their CVD risk because elevated LDL-c and decreased HDL-c both greatly increase the risk of developing CVD.⁵⁵ Moreover, T2DM patients' hyperglycemia and insulin resistance result in inflammation and OS, and dyslipidemia, which frequently plagues diabetic patients with HTN, linking it to vascular dysfunction and arterial stiffness.⁵⁶

Xanthine Oxidase and Uric acid

Comparison between HTN and T2DM Patients in XOD and SUA in Table 7.

Table 7. XOD and SUA in T2DM and HTN group.

Parameters	T2DM (30)	HTN (30)	p-value
XOD ng/l	34.51±9.94	26.8±7.44	0.121
Uric acid mg/dl	5.6±0.9	6.611±2.26	0.0353

For T2DM and HTN patients, there is no significant change in XOD. This outcome results maybe in HTN medications, which may alleviate OS.⁵⁷ Compared to T2DM patients, T2DM patients with HTN have a significantly higher SUA. Increased UA, HTN, and hyperglycemia had additional CVD risk factors. High SUA levels can cause OS, according to a number of in vitro and in vivo investigations.⁵⁸ Nitric oxide inhibition and endothelial dysfunction brought on by high SUA can result in diabetes and insulin resistance.⁵⁹

Conclusions

Dyslipidemia, OS reagents and hyperglycemia lead to many multiple risk factors for CVD and renal diseases. There is high BP in T2DM and abnormal lipids with increased SUA as a pathological situation. The release of ROS exceeds endogenous antioxidant capacity, leading to cell death. At cardiovascular levels, oxidative stress is highly implicated in myocardial infarction, ischemia/reperfusion, or heart failure.

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