Original Article

Oxidative DNA Damage and Lp (a) in Type 2 Diabetes Mellitus Patients with Cardiovascular Complication

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease presented with chronic blood glucose elevation and caused by decreased sensitivity to insulin. Diabetes is commonly linked with lipoprotein (a), a low-density lipoprotein particle, which considered as an independent risk factor for cardiovascular diseases. T2DM was correlated with increased oxidative stress that increases the risk of DNA damage. **Objective:** The current study aimed to estimate serum Lp (a) level and 8-hydroxydioxy-2-guanosine (8-OHdG) level in T2DM with cardiovascular complications. **Materials and Methods:** This case-control study included 80 T2DM patients; 41 patients presented with cardiovascular complications, while 39 patients were without any complications. Serum Lp (a) and 8-OHdG levels were evaluated for all patients using the enzyme-linked immunosorbent assay technique. **Results:** The mean age of complicated DM was 56.51 ± 5.75, with females being predominant (63.41%), and the majority of them (87.8%) were over than 50 years. Moreover, the mean duration of complicated DM was 14.29 ± 7.34 years. The mean levels of glucose (196.78 ± 62.63) and HbA1c (9.33 ± 1.81) were significantly higher in the group with complications compared to the uncomplicated group. The mean levels of 8-OHdG (198.00 ± 70.09) and Lp (a) (55.68 ± 14.14) were significantly higher among T2DM with complication compared to uncomplicated T2DM. **Conclusion:** The study found a higher mean serum Lp (a) and 8-OHdG among patients with DM and cardiovascular complications compared with those without cardiovascular complications.

Keywords: 8-Hydroxy-2-deoxyguanosine, cardiovascular complications, lipoprotein (a), type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) considered as a common lifelong metabolic and health problem presented with a chronic increase in blood glucose concentration and caused by an insulin action defect and/or insulin secretion defect.[1] Globally, it is the most challenging condition with a prevalence ranging between 5% and 20%.[2] Cardiovascular disorder associated with atherosclerosis is a major contributor to T2DM mortality and morbidity.[3-5] Atherosclerosis is a chronic inflammation of the intimal layer of the arterial wall with plaque accumulation that may result in death following its rupture.[6] Moreover, overweight and central obesity were found in 90% of type 2 diabetic patients and regarded as major risk factors for an increasing prevalence rate of cardiovascular complications in patients with T2DM as it has a role in insulin resistance development.[7,8] However, losing weight is considered a more predictor for reducing the incidence of DM and its complication by 30%–40%.[9]

The presence of both hyperglycemia and obesity in T2DM was associated with high oxidative stress that increases the hazard of DNA damage.[10] Oxidative stress is an imbalance between the generation of reactive oxygen species and antioxidant defense mechanisms, leading to increased production of free radicals with more diabetic complication development.[11] Oxidative DNA damage can be estimated by measuring

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8-hydroxydioxy-2-guanosine (8-OHdG) (nuclear and mitochondrial biomarker), which is regarded as the most sensitive and specific marker for DNA damage, as well as an early marker for endothelial dysfunction.[12-14] Lp (a) is produced by the liver and is considered a genetic variant of low density lipoprotein-cholesterol (LDL-C) particle, with bounding of one molecule of apo (a) covalently to a different molecule of apo B-100. It is found on chromosome 6q26-27.[15,16] Despite the presence of a controversial and unclear relationship between Lp (a) concentration and T2DM, there is a positive correlation between Lp (a) levels and coronary heart disease among patients with T2DM compared to those with normal glucose metabolism. This correlation is attributed to its structurally similar to LDL and its capability of undergoing oxidation reactions. Therefore, the increase in Lp (a) concentration regarded as an independent risk factor for the onset of atherosclerotic cardiovascular disease (ASCVD).[7]

Although a correlation between serum lipoprotein (a) levels and serum 8-OHdG levels has been reported in patients with T2DM,[17,18] limited information exists regarding the correlation between these two markers, particularly in type 2 diabetic patients with cardiovascular complications. Therefore, the present study aimed to estimate serum Lp (a) levels and evaluate the oxidized DNA damage by estimating serum 8-OHdG levels in individuals with T2DM, both with and without cardiovascular complications and to ascertain the correlation between serum Lp (a) levels and serum 8-OHdG levels in both groups.

Materials and Methods

Study design and subjects

This case-control study was performed to estimate serum oxidative DNA damage and lipoprotein (a) in individuals with T2DM, with 41 patients having cardiovascular complications as the case group and 39 T2DM patients without any complications as the control group. The ethical clearance has been obtained from the Directorate of Health of Duhok Governorate (16222022-1-3).

Exclusion criteria

Patients with pre-existing cardiovascular diseases, type 1 DM, chronic alcoholics, hepatitis, hypothyroidism, chronic kidney disease, and pregnant females were excluded in the study.

Data and measurement criteria

The data were collected using a standard questionnaire in the form of detailed history, clinical examination, and previous necessary investigations, along with the age of onset and time span of diabetes. The data of cardiovascular complications were obtained from patients who were previously diagnosed.

Biochemical measurements

Eight milliliters of venous blood samples were obtained from the participants after an overnight fast (3 mL in an ethylenediaminetetraacetic acid tube for HbA1c measurement and the remaining in gel separator tube for other parameters measurement). The samples in the gel tubes were centrifuged at 3400 rpm for 10 min, and the decanted supernatants were stored at −20°C until testing. Serum sugar, serum lipid profile, and blood HbA1c were immediately analyzed using the Cobas 6000 analyzer (Roche Diagnostics, Germany). Serum oxidative DNA damage and lipoprotein (a) were determined using enzyme-linked immunosorbent assay kit.

Anthropometric measurements

Waist circumference, height, and weight were measured using standard methods. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured for each patient.

Statistical analyses

The socio-demographic characteristics of patients with and without cardiovascular complications in T2DMwere presented as mean (standard deviation), median (interquartile range), or number (%). The comparisons of socio-demographic characteristics and biochemical measurements between T2DM patients with and without CVD complications were examined in an independent *t* test or Pearson Chi-squared tests. The DNA damage and Lp (a) levels in T2DM patients with and without CVD complications were analyzed using the Mann–Whitney *U* test and independent *t* test, respectively. The correlations between DNA damage, Lp (a), and biochemical measurements in T2DM patients with CVD complications were examined using bivariate regression analysis and presented in scatter plots. A significant level was set at a *P* value of <0.05. Statistical calculations were performed using JMP Pro 14.3.0.

Ethical approval

The study was conducted in accordance with the ethical principles based on the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 16222022-1-3 (February 16, 2022) to get this approval.

Results

Anthro-demographic and medical characteristics between complicated T2DM and uncomplicated T2DM are

detailed in Table 1. The mean age of individuals with complicated DM was 56.51 ± 5.75, with females being predominant (63.41%), and the majority of them (87.8%) were above 50 years of age. Moreover, the mean years duration of complicated DM was 14.29 ± 7.34, and there was a significantly higher mean waist circumferences (WC) (09.24 ± 8.12) among those with complicated DM.

Biochemical parameters of studied group are shown in Table 2. Mean levels of glucose (196.78 ± 62.63) and HbA1c (9.33 ± 1.81) were significantly higher in complicated group compared to uncomplicated group, whereas all other parameters differed with no statistically significant.

Table 3 shows serum level of Lp (a) and 8-OHdG among studied group. Both mean levels of 8-OHdG (198.00 ± 70.09) and Lp (a) (55.68 ± 14.14) were significantly higher among T2DM with complication compared to uncomplicated T2DM.

Discussion

To the best of our knowledge, the present study is the first to evaluate both serum Lp (a) levels and serum 8-OHdG levels among patients with T2DM complicated by cardiovascular diseases and to observe the relationship between them. While T2DM and elevated Lp (a) levels are considered independent risk factors for cardiovascular

Table 1: Comparisons of socio-demographic characteristics between T2DM patients with and without CVD complications

Socio-demographic characteristics	Study groups		*P* value (two-sided)
	T2DM without CVD complications (*n* = 39)	T2DM with CVD complications (*n* = 41)	
Age (years)	53.95 ± 7.96	56.51 ± 5.75	0.1016
<50	18 (46.15)	5 (12.20	**0.0007**
≥50	21 (53.85)	36 (87.8)	
Gender			0.2725
Male	19 (48.72%)	15 (36.59%)	
Female	20 (51.28%)	26 (63.41%)	
Disease duration (year)	8.36 ± 6.39	14.29 ± 7.34	**0.0002**
<5	17 (43.59%)	5 (12.20%)	**0.0125**
≥5	22 (57.13%)	36 (87.8%)	
Disease management			**0.0366**
Tablets alone	25 (64.10%)	19 (46.34%)	
Both insulin and tablets	14 (35.9%)	22 (53.66%)	
SBP	131.79 ± 14.67	131.88 ± 13.67	0.9800
DBP	84.17 ± 6.49	86.18 ± 6.72	0.1936
BMI	28.06 ± 5.03	29.93 ± 4.83	0.0973
WC (cm)	103.18 ± 11.94	109.24 ± 8.12	**0.0164**

An independent *t* test and Pearson Chi-squared tests were conducted for statistical analyses

The bold numbers show the significant differences

T2DM: type 2 diabetes mellitus, CVD: cardiovascular disease, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WC: waist circumferences

Table 2: Comparisons of biochemical measurements between T2DM patients with and without CVD complications

Socio-demographic characteristics	Study groups		*P* value (two-sided)
	T2DM without CVD complications (*n* = 39)	T2DM with CVD complications (*n* = 41)	
FBS (mg/dL)	167.39 ± 53.99	196.78 ± 62.63	**0.0298**
Cholesterol (mg/dL)	167.67 ± 34.30	168.90 ± 39.99	0.8827
HDL (mg/dL)	43.53 ± 9.29	44.46 ± 10.27	0.6727
LDL (mg/dL)	98.30 ± 30.35	106.25 ± 34.02	0.2795
T.G (mg/dL)	150.66 ± 63.39	159.51 ± 50.62	0.4996
HbA1c (%)	8.45 ± 1.68	9.33 ± 1.81	**0.0270**
<6.5	8 (20.51)	3 (7.32)	0.0867
≥6.5	31 (79.49)	38 (92.68)	

An independent *t* test and Pearson Chi-squared tests were conducted for statistical analyses

The bold numbers show the significant differences

T2DM: type 2 diabetes mellitus, CVD: cardiovascular disease, FBS: fasting blood sugar, HDL-C: high density lipoprotien- cholesterol, LDL-C: low density lipoprotien-cholesterol, TG: triglyceride, HbA1c: glycated hemoglobin

Table 3: Comparisons of 8-OHdG and Lp (a) between T2DM patients with and without CVD complications

Characteristics	Study groups (mean [SD])		*P* value (two-sided)
	T2DM without CVD complications ($n = 39$)	T2DM with CVD complications ($n = 41$)	
8-OHdG (ng/mL)	127.53 ± 57.4	198.00 ± 70.09	**0.0479**
Lp (a) (ng/mL)	49.88 ± 8.62	55.68 ± 14.14	**0.0471**

Mann–Whitney *U* test and independent *t* test were used for statistical analyses

The bold numbers show the significant differences

T2DM: type 2 diabetes mellitus, CVD: cardiovascular disease, SD: standard deviation, 8-OHdG: 8-hydroxydioxy-2-guanosine, Lp (a): lipoprotein (a)

disease development, the relationship between T2DM and Lp (a) level remains controversial and not clearly understood.[19-22] Considering that CVD remains the leading contributor to worldwide morbidity and mortality, early detection and management of high-risk individuals with T2DM and cardiovascular diseases are crucial in understating its underlying causes.[23-25]

The findings of this study suggest a strong and independent correlation between serum Lp (a) and the onset of ASCVD as there was a higher serum Lp (a) among patients with T2DM with cardiovascular disease; this can be explained briefly by many factors. First, oxidation of Lp (a) produces substrate-enhancing absorption of macrophage and foam cell formation.[26] Second, enhancement of cholesterol deposition in the atherosclerotic lesion as Lp (a) is more tightly bound to an extracellular matrix, such as fibrinogen and fibronectin, through its components [apo (a) and (B)], resulting in a buildup of the lipids in the arterial wall.[27,28] Third, Lp (a) enhances aggregation of the platelets and deactivation of inhibitor of the tissue factor pathway. Forth, it decreases plasminogen activity by the apo (a) component of Lp (a) as it has a similar structure to plasminogen, increasing the risk of thrombus formation.[29] There were conflicting results between different studies, as our observed finding was consistent with different studies done in a different part of the world that showed a direct connection between ASCVD risk and elevated serum Lp (a) level, and in contrast to other studies revealed no correlation between ASCVD risk and serum Lp (a) among patients with T2DM.[30,31]

Oxidative stress has a crucial role in the inflammatory response, change in vascular tone, and endothelial dysfunction development, and this leads to the development of atherosclerotic plaque.[32,33] The current study showed a significantly higher mean level of serum 8-OHdG as a marker for oxidative DNA damage among patients with T2DM complicated with cardiovascular diseases compared to uncomplicated T2DM. This is mostly related to the aging process, an increase in the inflammatory cytokines, obesity with insulin resistance, increased blood glucose concentration, and an increased blood HbA1c% in patients with T2DM that all related to increased incidence of cardiovascular complications among T2DM.[34-36] In chronic hyperglycemia, particularly in old-age diabetic patients, there is a consequence of metabolic changes such as auto-oxidation of glucose, glycation of protein, and polyol pathway stimulation, leading to the generation of reactive oxygen species and DNA damage that destroy endothelial function and atherosclerosis development.[37,38] Moreover, hyperglycemia results in the generation of hydrogen peroxide that enhance the release of iron from glycated hemoglobin which promote the generation of reactive oxygen species with more oxidative stress and more DNA damage with subsequent endothelial cell death and development of atherosclerotic plaque formation.[39]

In combination with another previous study, these results suggested that serum 8-OHdG is a strong biomarker to evaluate cardiovascular complications among patients with T2DM.[40] These findings provide evidence that increases oxidative stress and DNA damage in T2DM might contribute to the pathogenesis of diabetic complications.

Conclusion

The current study concluded that patients with cardiovascular complications in DM exhibited higher mean serum Lp (a) and 8-OHdG compared to those without cardiovascular complications. Moreover, the majority of diabetic patients with cardiovascular diseases were females over 50 years old and had a longer duration of DM than those without complications. More attention should be paid to individuals with T2DM who have elevated serum Lp (a) and 8-OHdG levels, as they may be associated with increased risk of developing CVD.

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Conflicts of interest

The author declares no conflict of interest.

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