

The Activity of Serum 8-Iso-Prostaglandin F₂ α as Oxidative Stress Marker in Patients with Diabetes Mellitus Type 2 and Associated Dyslipidemic Hyperglycemia

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Abstract

Background: Oxidative stress has been closely linked to the incidence of diabetic complications. Therefore, the aim of this research article was to study hyperglycemia and abnormal lipid profile in diabetic patient type 2 and its correlation with oxidative stress development as measured by 8-iso-PGF₂ α and 8-OHdG. **Methods:** Fifty (50) patients confirmed type 2 diabetes mellitus and eighty (80) non-diabetic control individuals were included in this study. All individuals were tested for blood glucose, lipid profile, 8-iso-PGF₂ α and 8-OHdG HdG. **Results:** The age of diabetic patients was observed to be ≥ 40 yrs in 96% and diabetes was frequently detected in female than in male patients (76% vs. 24%, $p < 0.0001$). Mean serum lipids were elevated in diabetic patients compared with control individuals ($p < 0.0001$) except in HDL-C, a significant decrease was recorded ($p = 0.04$). Serum 8-iso-PGF₂ α and 8-OHdG were elevated significantly in diabetic patients compared with non-diabetic control and a significant correlation was recorded between them ($r = 0.6$, $p < 0.0001$). 8-iso-PGF₂ α was associated with Age ($r = 0.394$, $p < 0.0001$), FBG (0.553, $p < 0.0001$), LDL-C ($r = 0.2$, $p = 0.023$), TG ($r = 0.176$, $p = 0.045$) and TC ($r = 0.2$, $p = 0.02$). Also, 8-OHdG was associated with age ($r = 0.558$, $p < 0.0001$), FBG ($r = 0.67$, $p < 0.0001$), LDL-C ($r = 0.28$, $p = 0.001$), TG ($r = 0.358$, $p < 0.0001$) and TC ($r = 0.33$, $p < 0.0001$). Age, FBG, HbA_{1c}, LDL-C, TG and TC showed a significant linear regression with 8-iso-PGF₂ α and 8-OHdG recording its role as significant predictors for the elevation of 8-iso-PGF₂ α and 8-OHdG. Therefore, hyperglycemia with oxidative stress development may play a role for dyslipidemia and diabetic complications. **Conclusion:** Di-

abetic patient's type 2 has a higher rate of abnormal serum lipids and correlates significantly with lipid peroxidation and oxidized DNA bases as measured by 8-iso-PGF2 α and 8-OHdG. Therefore, 8-iso-PGF2 α and 8-OHdG could be used as oxidative biomarkers for evaluating diabetic patients with early prediction of its complications and cancer development.

Keywords

Diabetes Mellitus Type 2, 8-iso-PGF2 α , 8-OHdG, ELISA, Abnormal Lipid Profile

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion and insulin action or both [1]. In type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.

Insulin resistance and type 2 diabetes are associated with a clustering of interrelated plasma lipid and lipoprotein abnormalities, which include reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglyceride levels. Each of these dyslipidemic features is associated with an increased risk of cardiovascular disease [2]. Insulin resistance has striking effects on lipoprotein size and subclass particle concentrations for VLDL, LDL and HDL [3] [4].

Oxidative stress due to overproduction of reactive oxygen species (ROS) has important role in prevention, initiation, and progression of chronic diseases from early childhood [5]. The considerable reactive properties of ROS cause oxidative damage to lipids, deoxyribonucleic acid (DNA), and proteins. Recent evidence suggests that ROS could have a role in the development of hypertension, dyslipidemia, diabetes mellitus, and atherosclerosis [6]. Oxidative stress status in diabetes could be clearly demonstrated by the increase of some specific biomarkers such as lipid hydroperoxides, DNA adducts and protein carbonyls [7].

Reactive oxygen species (ROS) can interact with DNA to produce damage including single- and double-stranded DNA breaks, deletions and nucleoside modifications. Among purine and pyrimidine base, guanine is more susceptible to oxidation. The hydroxyl radical can attack to C-8 position guanine and generate an oxidation product, 8-hydroxy deoxyguanine (8-OHdG) [8]. 8-OHdG, the oxidized form of the nucleoside 2'-deoxyguanosine present in DNA, is one of the most reliable and abundant markers of DNA damage because it reflects generalized cellular oxidative stress; it may be a risk factor for cancer, atherosclerosis and DM [6] [8].

Lipid peroxidation is most often measured using malondialdehyde (MDA) and 8-isoprostaglandin F2 α (8-iso-PGF2 α) [9] [10] [11]. Isoprostanes are stable products of arachidonic acid peroxidation due to free radical activity and reliable biomarkers for oxidative stress, which are suitable for measuring lipid peroxidation in place of malondialdehyde (MDA) [12]. Isoprostanes, including 8-iso-PGF2 α are stable in biological fluids

and easily detectable as well as not being affected by diet and modulated by endogenous antioxidants [13].

The measurement of bioactive F2-IsoPs levels offers a unique noninvasive analytical tool to study the role of free radicals in physiology, oxidative stress-related diseases, and acute or chronic inflammatory conditions [14]. Elevated F2-IsoP levels have been associated with multiple chronic conditions which commonly have been interpreted as an etiological link between oxidative stress and the disease; specifically, type 2 diabetes and its risk factors, such as obesity, impaired glucose tolerance, and insulin resistance [15]. Therefore, the objective of this research article was to study hyperglycemia and abnormal lipid profile in diabetic patients and its correlation with oxidative stress development as detected by 8-iso-PGF2 α and 8-OHdG.

2. Subjects and Methods

2.1. Subjects

Fifty (50) patients confirmed type-2 diabetes mellitus (12 males and 38 females; mean age 51.04 ± 7.49 yrs) and eighty (80) non-diabetic control individuals (52 males and 28 females; mean age 39.7 ± 10.1 yrs) were included in this study. This study was done in collaboration between biochemistry department, faculty of medicine, Umm Al-Qura University, Makkah Al-Mukarama, Kingdom of Saudi Arabia and Gastroenterology surgical center, Mansoura University, Mansoura, Egypt from 2014-2016. The study protocol was approved by Ethics Review Board for Human Studies at Faculty of Medicine, Umm Al-Qura University and conformed to the ethical guidelines of the 1975 Helsinki declaration.

All participants underwent a clinical examination and a questionnaire including medical and family history. The exclusion criteria were for those with past history of type-1 diabetes, cancer, cardiovascular or renal diseases. Blood samples were obtained following at least 8 hours fasting period according to the American Diabetes Association criteria; only patients with fasting blood glucose above 126 mg/dl or postprandial two hours after meal above 200 mg/dl were included [16]. Blood samples were collected for blood glucose analysis and serum was immediately separated by centrifugation at 3000 rpm for 10 min and stored at 4°C until processed for lipid analysis and oxidative biomarkers (8-OHdG and 8-iso-PGF2 α).

2.2. Measurement of Biochemical Parameters

Fasting blood sugar (FBS), postprandial blood sugar (PBS), Triglycerides (TG), total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) were measured with an autoanalyzer (COBAS INTEGRA 400PLUS, Roche, Germany) using commercial kits. Serum LDL-C was calculated according to the computational formula of Friedewald *et al.* [17] [LDL = TC-HDL-TC/5.0 mg/dl]. Castelli index [18] was used for determining the ratio between total cholesterol and HDL-C.

Dyslipidemia (Abnormal lipid profile) was defined using the National cholesterol Education program Adult treatment panel III (NCEP-ATP III) [19]. In addition, he-

moglobinA1c (HbA1c %) was measured according to DCCT (Diabetes Control and Complications Trial) [20].

2.3. Serum 8-Iso-PGF2 α

8-iso-PGF2 α was measured by direct 8-iso-PGF2 α ELISA kit (Enzo Life Sciences Inc., Switzerland). The direct 8-iso-PGF2 α ELISA kit is a competitive immunoassay for the quantitative determination of 8-iso-PGF2 α in biological fluids [21]. The kit uses a polyclonal antibody to 8-iso-PGF2 α to bind in a competitive manner with 8-iso-PGF2 α in the sample or 8-iso-PGF2 α covalently attached to alkaline phosphatase. After incubation, the excess reagents were washed away and substrate was added. The generated yellow color was read at 405 nm and the intensity of the bound yellow color is inversely proportional to the concentration of 8-iso-PGF2 α in either standard or sample. The measured optical density is used to calculate the concentration of 8-iso-PGF2 α from the calibration curve.

2.4. Serum 8-OHdG

Serum 8-OHdG was measured using an ELISA kit (Cloud-clone Corp., Assembled by USCo life science inc. USA). This assay employs the competitive inhibition enzyme immunoassay technique. Pre-coated microplate with 8-OHdG monoclonal antibody used for competitive inhibition reaction between biotin-labeled 8-OHdG and unlabeled 8-OHdG. After incubation, the unbound conjugate is washed off with subsequent addition of avidin conjugated horse radish peroxidase (HRP) followed by substrate solution. The intensity of the developed color is reversely proportional to the concentration of 8-OHdG in the sample. The detection range was from 74.07 to 6,000 pg/ml.

2.5. Statistical Analysis

Data was analyzed using SPSS (version 17, Sydney, NSW, Australia). Statistical analysis was performed using independent sample test for parametric variables and Chi-square for categorical variables. Relationship between variables was detected by Pearson's correlation coefficient and linear regression analysis was performed to analyze 8-OHdG and 8-iso-PGF2 α as dependent variables. Quantitative data was expressed as mean \pm SD and qualitative data as frequencies and percentages.

3. Results

General characteristics and biochemical markers of the study group were listed in **Table 1**. Diabetic patients were aged < 40 yrs in 4%, 40 - 49 yrs in 42%, 50 - 59 yrs in 42% and \geq 60 yrs in 12%. Diabetes was more frequently detected in female than in male patients (76% vs. 24%, $p < 0.0001$). Hyperglycemia as measured by FBG, PPG and HbA1c showed significant elevation in diabetic patients compared to non-diabetic control (184.4 ± 56.9 mg/dl, 328.1 ± 75.7 mg/dl, $7.06 \pm 0.7\%$ vs. 80.97 ± 6.78 mg/dl, 97.78 ± 10.1 mg/dl, $3.7 \pm 0.6\%$ respectively, $p < 0.0001$).

Mean serum lipids showed significant elevation in diabetic patients compared to

Table 1. General characteristics and biochemical markers of all participants in the study group.

Variable	Diabetic Patients (n = 50)	Non-Diabetic Control (n = 80)	p value *
Sex	38/12	28/52	
F	38 (76%)	28 (35%)	<0.0001
M	12 (24%)	52 (65%)	
Age (yrs)	51.04 ± 7.49	39.7 ± 10.1	
<40	2 (4%)	46 (57.5%)	
40 - 49	21 (42%)	19 (23.75%)	<0.0001
50 - 59	21 (42%)	13 (16.25%)	
≥60	6 (12%)	2(2.5%)	
FBG (mg/dl)	184.4 ± 56.9	80.97 ± 6.78	<0.0001
PPG (mg/dl)	328.1 ± 75.7	97.78 ± 10.1	<0.0001
HbA1c (%)	7.06 ± 0.7	3.7 ± 0.6	<0.0001
Lipid profile (mg/dl)			
TG	142.4 ± 63.6	98.4 ± 37.58	<0.0001
TC	222.6 ± 37.87	193.4 ± 22.27	<0.0001
HDL-C	48.84 ± 9.49	52.5 ± 10.15	0.04
LDL-C	144.56 ± 34.8	120.8 ± 18.6	<0.0001
TC/HDL-C	4.7 ± 1.2	3.8 ± 0.6	0.001

*p value is significant < 0.05; Abbreviations: FBG (Fasting blood glucose), HbA1c (Glycated hemoglobin), LDL-C (Low density lipoprotein-cholesterol), HDL-C (High density lipoprotein-cholesterol), TG (Triglycerides), TC (Total cholesterol).

non-diabetic control individuals except in HDL-C a significant decrease was recorded (**Table 1**). LDL-C, TG and TC were elevated significantly in diabetic patients compared to non-diabetic control (144.56 ± 34.8 , 142.4 ± 63.6 , 222.6 ± 37.87 mg/dl vs. 120.8 ± 18.6 , 98.4 ± 37.58 , 193.4 ± 22.27 mg/dl respectively, $p < 0.0001$). TC/HDL-C showed also significant elevation in diabetic patients compared to non-diabetic control (4.7 ± 1.2 vs. 3.8 ± 0.6 mg/dl, $p = 0.001$) but in HDL-C, a significant decrease was recorded (48.84 ± 9.49 vs. 52.5 ± 10.15 mg/dl, $p = 0.04$).

Abnormal serum lipids was recorded in diabetic patients with a significant difference compared to non-diabetic control as regard to LDL-C (56% vs. 28.8%, $p = 0.002$), TG (28% vs. 5%, $p < 0.0001$), TC (76% vs. 38.8%, $p < 0.0001$) and TC/HDL-C (68% vs. 46.3%, $p = 0.015$) but the difference in abnormal HDL-C (60% vs. 56.3%, $p = 0.7$) was not significant (**Table 2**).

Hyperglycemia as measured by FBG and HbA1c was correlated significantly with serum lipids (**Figure 1**). FBG showed a significant positive correlation with LDL-C ($r = 0.411$, $p < 0.0001$) and TG ($r = 0.32$, $p < 0.0001$). HbA1c showed a significant positive correlation with LDL-C ($r = 0.409$, $p < 0.0001$) and TG ($r = 0.401$, $p < 0.0001$) but with HDL-C, a significant negative correlation was recorded ($r = -0.17$, $p = 0.05$).

Oxidative stress biomarkers 8-iso-PGF2 α and 8-OHdG in the sera of diabetic patients and control individuals were listed in **Table 3**. Diabetic patients showed significant elevation of serum 8-iso-PGF2 α (2719.38 ± 1864.68 vs. 951.45 ± 669.44 pg/ml, $p < 0.0001$) and 8-OHdG (178.35 ± 26.23 vs. 110.2 ± 31.46 pg/ml, $p < 0.0001$) compared to

Table 2. Abnormal serum lipids among all participants in the study group.

Group variable	Abnormal lipid profile [†]				
	LDL-C	HDL-C	TC	TG	TC/HDL-C
Diabetic Patients (n = 50)	28 (56%)	30 (60%)	38 (76%)	14 (28%)	34 (68%)
Non-Diabetic Control (n = 80)	23 (28.8%)	45 (56.3%)	31 (38.8%)	4 (5%)	37 (46.3%)
p value*	0.002	0.7	<0.0001	<0.0001	0.015

*p value is significant < 0.05; [†]Abnormal lipid profile was defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [19]. Abbreviations: LDL-C (Low density lipoprotein-cholesterol), HDL-C (High density lipoprotein-cholesterol), TC (Total cholesterol), TG (Triglycerides).

Table 3. Incidence of 8-iso-PGF2 α and 8-OHdG in all participants of the study group.

Variable	Diabetic Patients (n = 50)	Non-Diabetic Control (n = 80)	p value *
8-OHdG (pg/ml)	178.35 \pm 26.23	110.2 \pm 31.46	<0.0001
8-iso-PGF2 α (pg/ml)	2719.38 \pm 1864.68	951.45 \pm 669.44	<0.0001

*p value is significant < 0.05; 8-iso-PGF2 α (8-iso-prostaglandin F2 α); 8-OHdG (8-hydroxy deoxyguanosin).

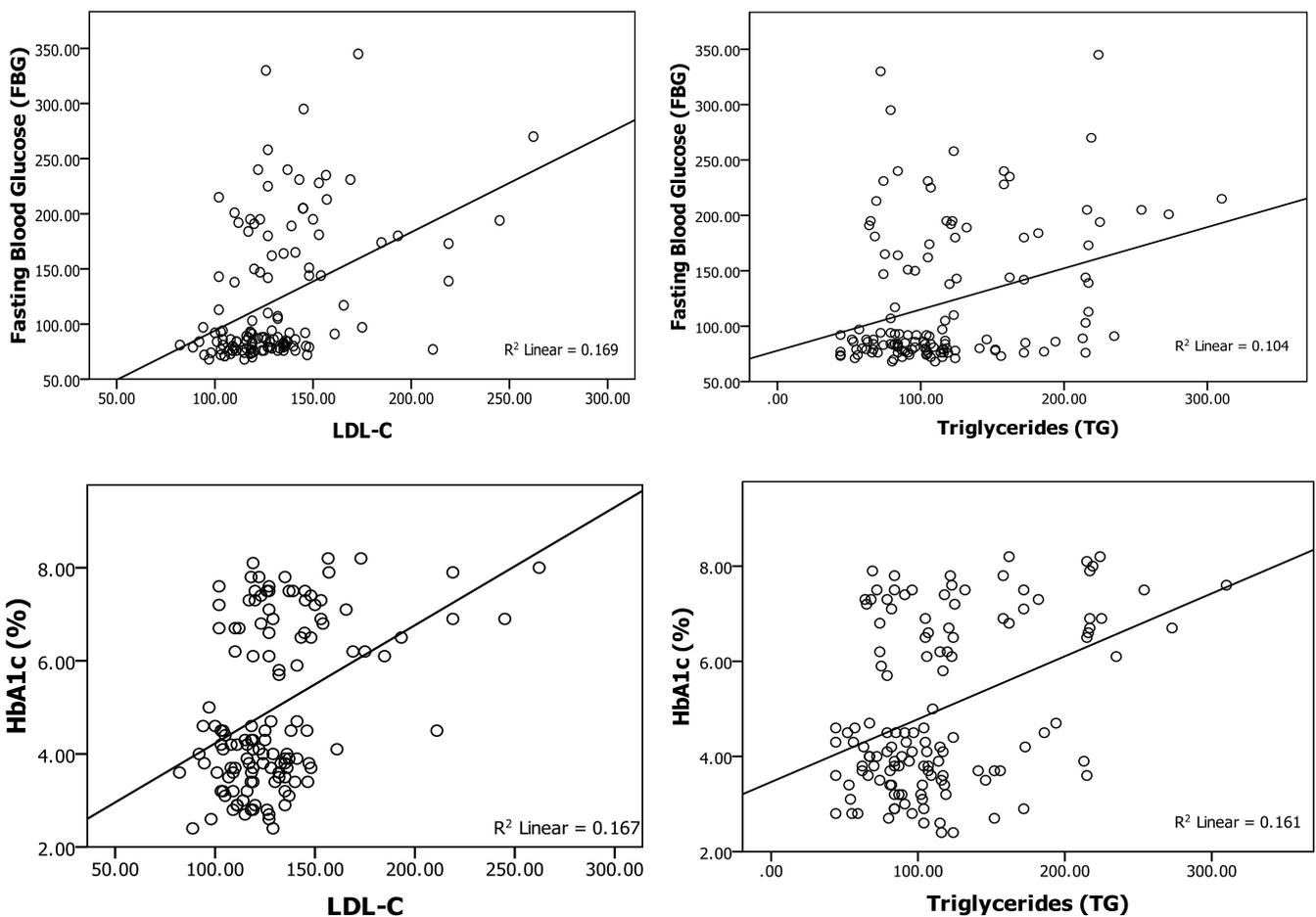


Figure 1. Correlation between Fasting blood glucose (FBG) and HbA1c with Low density lipoprotein-Cholesterol (LDL-C) and Triglyceride (TG) in all participants.

control individuals. 8-iso-PGF2 α and 8-OHdG were associated significantly ($r = 0.6$, $p < 0.0001$) in all participants (**Figure 2**).

Pearson correlation of 8-OHdG and 8-iso-PGF2 α with age, hyperglycemia and lipid profile were recorded in **Table 4**. 8-iso-PGF2 α showed a significant positive correlation with Age ($r = 0.39$, $p < 0.0001$), HbA1c ($r = 0.589$, $p < 0.0001$), FBG ($r = 0.55$, $p < 0.0001$), LDL-C ($r = 0.2$, $p = 0.023$), TG ($r = 0.176$, $p = 0.045$) and TC ($r = 0.2$, $p = 0.02$). Also, a significant positive correlation was detected between 8-OHdG and Age ($r = 0.558$, $p < 0.0001$), FBG ($r = 0.67$, $p < 0.0001$), HbA1c ($r = 0.76$, $p < 0.0001$), LDL-C ($r = 0.28$, $p = 0.001$), TG ($r = 0.36$, $p < 0.0001$) and TC ($r = 0.33$, $p < 0.0001$). However, with HDL, negative correlation was detected insignificant with both 8-OHdG and 8-iso-PGF2 α .

Multiple linear regressions of 8-iso-PGF2 α and 8-OHdG with various independent variables (**Table 5**) showed that Age, FBG, HbA1c, LDL-C, TC and TG were recorded as significant predictors for the elevation of 8-OHdG and 8-iso-PGF2 α .

Table 4. Pearson’s correlation of 8-OHdG and 8-iso-PGF2 α with Age, FBG, HbA1c, and lipid profile.

	Age	FBG	HbA1c	LDL-C	HDL-C	TC	TG	TC/HDL-C
8-iso-PGF2 α	0.394 ^a	0.553 ^a	0.589 ^a	0.20 ^a	-0.107	0.203 ^a	0.176 ^b	0.233 ^a
	0.0001	0.0001	0.0001	0.023	0.226	0.021	0.045	0.008
8-OHdG	0.558 ^a	0.671 ^a	0.761 ^a	0.287 ^a	-0.145	0.332 ^a	0.358 ^a	0.352 ^a
	0.0001	0.0001	0.0001	0.001	0.09	0.0001	0.0001	0.0001

^aCorrelation is significant at the 0.01 level (2tailed); ^bCorrelation is significant at the 0.05 level (2tailed); Abbreviations: FBG (Fasting blood glucose), HbA1c (Glycated hemoglobin), LDL-C (Low density lipoprotein-cholesterol), HDL-C (High density lipoprotein-cholesterol), TC (Total cholesterol), TG (Triglycerides).

Table 5. Multiple linear regressions of 8-iso-PGF2 α and 8-OHdG with various independent variables.

	Age	FBG	HbA1c	LDL-C	HDL-C	TG	TC
8-iso-PGF2 α							
R	0.39	0.55	0.589	0.2	0.107	0.176	0.203
R ²	0.155	0.306	0.347	0.04	0.01	0.03	0.04
P*	<0.0001	<0.0001	<0.0001	0.023	0.226	0.045	0.02
B ^f	56.4	13.69	511.9	10.76	-16.3	5.03	9.56
(95% CI)	(33.4 - 79.4)	(10.09-17.31)	(389.1 - 634.7)	(1.51 - 19.99)	(-42.8 - 10.24)	(0.11 - 9.95)	(1.5 - 17.6)
8-OHdG							
R	0.558	0.67	0.761	0.287	0.145	0.358	0.332
R ²	0.312	0.45	0.58	0.08	0.02	0.128	0.11
P*	<0.0001	<0.0001	<0.0001	0.001	0.09	<0.0001	<0.0001
B ^f	2.32	0.48	19.21	0.449	-0.64	0.297	0.46
(95% CI)	(1.72 - 2.9)	(0.39 - 0.58)	(16.4 - 22.07)	(0.19 - 0.71)	(-1.4 - 0.123)	(0.16 - 0.43)	(0.23 - 0.68)

*p value is significant < 0.05; ^fB indicates standardized partial regression coefficient; Variables included: Age, FBG (Fasting blood glucose), HbA1c (Glycated hemoglobin), LDL-C (Low density lipoprotein), HDL-C (High density lipoprotein), TG (Triglycerides), TC (Total cholesterol).

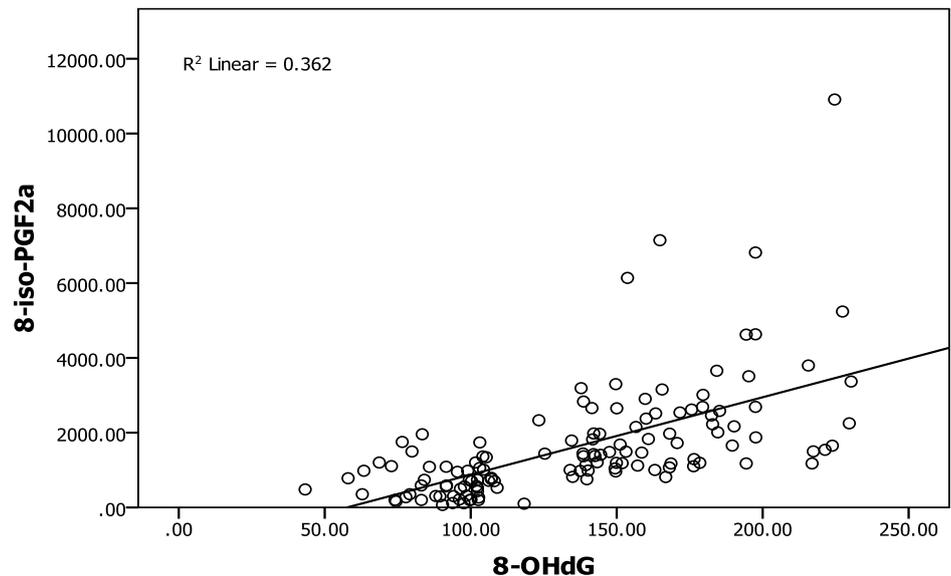


Figure 2. Correlation between 8-OHdG and 8-iso-PGF2 α in all participants ($r = 0.6$, $p < 0.0001$).

4. Discussion

Diabetes is a major source of morbidity, mortality and economic cost to society [22]. Despite well-controlled blood glucose, diabetic complications still inevitably take place via several mechanisms including excessive generation of free radicals in patients who suffer from diabetes mellitus (DM) [7]. Therefore, this research article was conducted to study hyperglycemia and abnormal lipid profile in diabetic patients and its correlation with oxidative stress development as measured by 8-iso-PGF2 α and 8-OHdG.

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity [23]. The age of diabetic patients in our study was observed to be ≥ 40 yrs in 96% proving that age plays a significant role in the risk of developing type 2 DM especially after 40 yrs [24]. However, it has been observed that insulin secretion declines with advancing age, and this decline may be accelerated by genetic factors [25].

Diabetes is a disease characterized by poor glycemic control [26]. Hyperglycemia generates reactive oxygen species (ROS), which in turn cause damage to the cells in many ways [27] [28]. OS can simultaneously result damage in biomolecules including lipids, proteins, nucleic acids and carbohydrates [29]. Lipids are reported as one of the primary targets of ROS [30]. Isoprostanes are a recently discovered group of prostaglandin isomers. Results of previous studies suggest that they can be used as oxidative stress markers, because in a number of cardiovascular, pulmonary and neurological diseases, their levels in biological samples considerably increase [31].

Jelinek *et al.* [32] demonstrated a significant increase in 8-iso-PGF2 α in the IFG group and supports the findings that, 8-iso-PGF2 α was increased following an oral glucose tolerance in individuals with no diabetes but with either IFG or impaired glucose tolerance [33]. 8-iso-PGF2 α was elevated in the sera of diabetic patients (2719.38 ± 1864.68 pg/ml) in current study compared with non-diabetic control (951.45 ± 669.44

pg/ml, $p < 0.0001$). Similar results were recorded by Gopaul *et al.* [34], that, the plasma levels of 8-iso-PGF 2α in non-insulin dependent diabetes mellitus (NI-DDM, diabetes type 2) were higher ($N = 39$, 0.49 - 2.16 nM) than in the control group ($N = 16$, 0.02 - 0.63 nM) and by Davi *et al.* [35] in urine samples, that 8-iso-PGF 2α in patients with NID-DM (419 ± 208 pg/mg creatinine) were significantly higher ($p = 0.0001$) than in age-matched healthy subjects (208 ± 92 pg/mg creatinine).

A clinical study performed by Bandeira and coworkers [36] aimed at characterizing blood oxidative stress in diabetic patients, reported a significant higher lipid peroxidation which showed a close relationship with high glucose levels as observed by the fasting glucose and HbA1c levels. This observation are in consistent with our findings in diabetic patients, that higher lipid peroxidation as measured by 8-iso-PGF 2α showed a close relationship with FBG ($r = 0.553$, $p < 0.0001$) and HbA1c ($r = 0.6$, $p < 0.0001$). Therefore, increased lipid peroxidation presents a close relationship with the high glycaemic levels and oxidative stress in diabetes mellitus [36] [37].

Changes in serum lipids have been demonstrated in the IFG stage and are associated with oxidation of arachidonic acid to 8-iso-PGF 2α [38] [39]. Changes in serum lipids was demonstrated in diabetic patients of our study and a significant association was recorded with 8-iso-PGF 2α . Serum lipids showed significant elevation in diabetic patients ($p < 0.0001$) but in HDL-C, a significant decrease ($p = 0.04$) was recorded confirming other reports [32] demonstrated a significant reduction in both total cholesterol and HDL-C which explains the increased 8-iso-PGF 2α as HDL-C carries 8-iso-PGF 2α [10].

Like the oxidation of lipids and proteins, the oxidation of DNA reveals information on the overall state of the system being investigated. DNA oxidation is of particular concern for mitotic tissues, where increases in DNA mutations are believed to increase risk for cancer development [40]. Oxidized DNA as measured by 8-OHdG in our study was elevated significantly ($p < 0.0001$) in diabetic patients compared with non-diabetic control referring to the risk in DNA oxidative damage and cancer development. Therefore, data collected by measurement of oxidized DNA bases in serum or excreted in urine, most notably 8-OHdG have served as a biomarker for carcinogenesis [41].

8-OHdG has been suggested to serve as a new sensitive biomarker of the in vivo oxidative DNA damage in diabetes [42]. In current study, 8-OHdG in diabetic patients was associated with hyperglycemia and abnormal serum lipids. LDL showed significant elevation in diabetic patients and the correlation with 8-OHdG was highly significant ($r = 0.28$, $p = 0.001$) on contrary with other reports [43]. Lower HDL-C was detected in diabetic patients more frequently than in non-diabetic control ($p = 0.04$) but negative correlation with 8-OHdG was detected insignificant consisting with the finding of Taskinen [44] and on contrary with the conclusion of Abdel-Aal *et al.* [45] that lower HDL-C showed significant negative correlation with 8-OHdG. Reduced HDL-C in diabetic subjects result from higher catabolic rate of HDL-C with normal activity of cholesterol ester transfer protein and hepatic lipase in insulin resistance conditions [45].

The good correlation between 8-OHdG and isoprostanes in diabetic patients was well

documented by Harman *et al.* [46] and in our report ($r = 0.6$, $p < 0.0001$). However, some researchers [47] reported the elevated levels of 8-OHdG and 8-iso-PGF2 α in the diabetics, although these studies have not shown the association between them. The association of 8-iso-PGF2 α and 8-OHdG with hyperglycemia (FBG and HBA1c), elevated LDL-C and triglycerides in diabetic patients of our study was confirmed by other studies [43] [48] reflecting a generalized cellular oxidative stress which may be a risk factor for diabetic complication and cancer development as suggested by Brownlee [49] that hyperglycemia-induced overproduction of superoxide, plays a critical role in the biochemical abnormalities leading to vascular disease and diabetic complications. Therefore, serum 8-OHdG and 8-iso-PGF2 α could be used for early prediction of diabetic complications and cancer development as urinary 8-OHdG and 8-iso-PGF2 α excretions have been measured in many studies because they are associated with cancer development and advancement of diabetes and atherosclerosis [50].

5. Conclusion

Diabetic patient's type 2 has a higher rate of abnormal lipid profile and correlates significantly with oxidative stress as measured by 8-iso-PGF2 α and 8-OHdG. Therefore, 8-iso-PGF2 α and 8-OHdG could be used as oxidative biomarkers for evaluating diabetic patients with early prediction for its complications and cancer development.

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Authors' Contributions

All authors equally contributed in the article. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests regarding the publication of this manuscript.

Declarations

- Ethics approval and consent to participate: The study protocol was approved by Ethics Review Board for Human Studies at Faculty of Medicine, Umm Al-Qura University and conformed to the ethical guidelines of the 1975 Helsinki declaration.
- Availability of data and material: The dataset(s) supporting the conclusions of this article is (are) included within the article and its additional files.
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Limitations

- Although this is an attempt to study oxidative biomarkers that might be of significance in progression of diabetic patients, only a limited number of cases were investigated here.
- Since the prognosis of diabetes type 2 remains poor and identification of useful molecular prognostic markers for diabetic complications is required, follow up of diabetic patients must be studied in further study.
- Other risk factors like obesity might be of significance in the progression of diabetic complications and must be studied in further study.

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Abbreviation Note List

DM type 2: Diabetes mellitus type 2
FBG: Fasting blood glucose
PBS: Postprandial blood glucose
HbA1c: hemoglobina1c
HDL-C: High density lipoprotein-cholesterol
LDL-C: Low density lipoprotein-cholesterol
VLDL: Very low density lipoprotein
TG: Triglycerides
TC: Total cholesterol
DNA: Deoxyribonucleic acid
8-iso-PGF2 α : 8-iso-prostaglandin F2 α
8-OHdG: 8-hydroxy deoxyguanosin
ROS: Reactive oxygen species
HRP: Horse radish peroxidase
DCCT: Diabetic control and complications trial
ELISA: Enzyme linked immunosorbent assay
IFG: Impaired Fasting glucose
NI-DDM diabetes type 2: Non insulin-dependent diabetes mellitus type 2



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