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Case Report

Role of oxidized LDL (ox-LDL) and adhesion molecules (VCAM-1, ICAM-1) in type 2 diabetes mellitus with a potential for atherosclerotic complications in patients of Qassim region, KSA

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Abstract

Background: Type-2 diabetes mellitus (type 2 DM) is powerful and independent risk factors for coronary artery disease, stroke, and peripheral arterial disease. Accelerated atherosclerosis is the major vascular complication of diabetes, constituting the main cause of morbidity and mortality in this common metabolic disorder. The role of oxidized low density lipoprotein (Ox-LDL) and cell adhesion molecules (CAMs) in diabetic complications as atherogenesis is unclear and available studies are contradictory.

Objectives: The current study was conducted to investigate the pathological role of oxLDL and cell adhesion molecules (VCAM-1 and ICAM-1) and their clinical impact in type 2 DM patients.

Patients and Methods: The serum levels of ox-LDL and VCAM-1 and ICAM-1 were measured by enzyme-linked immunosorbent assay. Their levels were correlated to glycemic status and lipid profile in 60 type 2 diabetic patients compared to 25 healthy subjects.

Results: The current study revealed a significant higher ox-LDL and VCAM-1 levels in diabetic patients compared to healthy group, with significant higher levels of oxLDL in uncontrolled diabetes compared to controlled diabetes. The elevation of ox-LDL in DM patients ($p < 0.001$) was more profound than LDL elevation ($P<0.05$). Ox-LDL was correlated positively with glycemic index (HbA1c and FBG), lipid profile (TG, LDL and atherogenic index), blood pressure (systole and diastole) and with VCAM-1. Moreover, VCAM-1 was positively correlated to HbA1c, cholesterol and ICAM-1.

Conclusion: The elevated levels of ox-LDL and VCAM-1 in DM versus controls and their positive correlation suggest the potential role of ox-LDL as a possible etiological and prognostic marker for atherosclerosis. Moreover anti- ox-LDL drugs may be tried as new therapeutic agents to minimize atherosclerotic complications of DM

INTRODUCTION

Diabetes mellitus (DM) is a major risk factor for atherosclerosis as hyperglycemia-induced endothelial dysfunctions, along with hypercoagulable potential of DM, so accelerate the process of athero-thrombotic complications [1]. Atherosclerosis is responsible for 80% of all deaths among diabetic patients. The mechanism(s) linking premature endothelial damage and macrovascular disease in insulin-resistant Type 2 diabetes is at present not fully understood [2].

Cardiovascular (CV) morbidity is a major burden in patients with type 2 DM with endothelial dysfunction as an early sign of diabetic vascular disease [3]. Elevated oxidized low-density lipoprotein (oxLDL), formed within the arterial wall, and is commonly seen as part of the atherogenic profile [4]. Van den Oever el

al. [5] reported that oxLDL increased the adhesion of monocytes to human coronary smooth muscle cells, whereas native LDLs had no effect. Oxidized LDL contributes to many atherogenic steps in the vascular wall, but the significance of oxLDL in circulating blood remains unclear [6]. It is proved that, hyperglycemia of diabetic patients can trigger endothelial damage through increased oxidative stress with formation of oxLDL and upregulation of cellular adhesion molecules [7]. Cellular adhesion molecules (CAMs), namely intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), are poorly expressed by the resting endothelium, but are unregulated during inflammatory atherogenesis and may be an index of endothelial activation or even a molecular marker of early atherosclerosis. Studies in these areas may generate new strategies for treatment of cardiovascular diseases [8,9].

The mechanism by which ox-LDL can accelerate the atherogenic process is unknown, the purpose of the present study was to correlate between susceptibility of LDL to oxidation and the concentration of CAMs in type 2 diabetes. To achieve this goal, we measured levels of ox-LDL in type 2 diabetic patients and correlated its level to atherosclerosis by detecting lipid parameters and atherosclerosis index (calculated from lipid profiles), ICAM-1 and VCAM-1 (as markers of endothelial integrity that trigger atherosclerosis), and glycemic status.

MATERIAL AND METHODS

The current study included 60 Saudi patients with type 2 DM, they were recruited from the Outpatient Clinic of Qassim University, Buraidah, Qassim, KSA during the period from May to September, 2011. The patients were further classified based on their glycosylated hemoglobinA1c (HbA1c) into; 31 controlled diabetic patients (mean age: 45.6 ± 9.3 years) with (HbA1c ≤7 %) and 29 uncontrolled diabetic patients (mean age: 54.6 ± 17.3 years) with (HbA1c>7%). They were treated with oral hypoglycemic drugs or complementary insulin therapy. Their results were compared to 25 healthy control volunteer subjects (44.8 ± 14.8 years) with matched age and sex. All individuals were subjected to complete full history and clinical examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m2). An informed consent was obtained from all included subjects, and the study was approved from the local ethics committee.

Exclusion criteria: Patients taking medications affecting glucose metabolism like cortisone, were excluded.

Samples: Blood samples (5 to 10 ml) were drawn after 10-12 hours of fasting. Samples were divided into two parts: One part was taken on Na_2-EDTA tubes (final concentration 1mg/mL) for HbA1c% determination, the other part was taken into clotted tubes, where sera were obtained by centrifugation at 3000 rpm for 10 minutes. Serum were separated into two aliquots; one for measurement of fasting blood sugar immediately while the other aliquot was stored at -20°C until measurements of other parameters described in the study.

Laboratory investigations

Fasting plasma glucose (FBG) was measuredby colorimetric methods; using kits provided byBeckman Instruments, Inc., Brea, USA [10]. HbA1c was detected by colometric assay after chromatography separation (Procedure No. 0350, Helena Laboratories, CA,USA)[11]. Lipid profile parameters were evaluated, including total cholesterol (TC) [12], high density lipoprotein cholesterol (HDL-c) [13] and triglyceride (TG) [14]. They were determined using kits provided by StanbioLiquiColor Procedure, USA. LDL-cholesterol was calculated as follows: LDL= Total Cholesterol - HDL - TG/ 5 [15].Atherogenic index was calculated as follows: Atherogenic index = log [TG / HDL] [16] .

sICAM-1 and sVCAM-1 were measured by an enzyme-linked immunosorbent assay using Human ELISA kits (Quantikine, R&D system, Minneapolis, USA) [7]. Ox- LDL was measured by an enzyme-linked immunosorbent assay using Human Ox- LDL ELISA kits (DRG International Inc., USA) [17].

Statistical Analysis

The analysis was done using the Statistical Package for the Social Sciences (SPSS Statistical software version 16). Clinical and laboratory data were presented means ± SE and/or median and mean rank. Statistical comparison was made using the parametric test, Anova (followed by post Hoc test) or non-parametric test Mann-Whitney U (to compare two groups) and Kruskal-Wallis test (to compare three groups). Chi-square test ($\chi 2$) was used to compare qualitative parameters (age, sex...) between groups. Correlation between different variables was performed by Pearson`s correlation coefficient test. Statistical significant was set at a value $P < 0.05$.

RESULTS

Table 1 depicts the demographic data of the study groups. The BMI showed no significant difference among healthy and diabetic groups, while uncontrolled diabetic patients had significantly higher BMI than healthy group ($P<0.05$). Furthermore, the blood pressure (systolic and diastolic) was significantly

higher in diabetic patients compared to healthy group (P< 0.05), moreover, uncontrolled diabetes group showed higher levels than controlled ones. The descriptive statistics of glycemic status and lipid profile parameters are shown in table (2). FBG, TG, LDL and atherogenic index were significantly higher in diabetic patients compared to healthy control group (P< 0.05). Meanwhile, FBG, HbA1c and cholesterol showed significant higher levels in uncontrolled compared to controlled diabetic patients (P<0.05).

Ox-LDL and VCAM-1 showed significant higher levels in all diabetic patients (n=60) than in healthy group while ICAM-1 didn't show any difference between both groups (table 3). Furthermore, uncontrolled diabetic patients had higher ox-LDL levels compared to controlled ones (p<0.001, Table 4).

Correlation analysis among the investigated serum parameters revealed a significant positive correlation between Ox-LDL with advancing age of patients (p<0.05), systolic and diastolic blood pressure, FBG (P<0.01), HbA1C (p<0.05), TG (P<0.05), LDL (p<0.01), atherogenic index (p<0.05) and with VCAM-1 (p<0.05). Meanwhile, VCAM-1 was correlated to HbA1C (p<0.05), cholesterol (p<0.05), and with ICAM-1(p<0.01). Furthermore, ICAM-1 was significantly correlated to FBS (p<0.05) and cholesterol (p<0.05, table 5).

Table 1. Demographic data of the study groups

Parameters	Healthy Control	Controlled DM	Uncontrolled DM
Age *(Mean± SD)*	44.8 ± 14.8	45.6 ± 9.3	54.6 ± 17.3
Sex			
Male (%)	12 (48%)	11 (35.8%)	12 (46.2%)
Female (%)	13 (52%)	18 (64.5%)	19 (53.8%)
BMI (kg/m^2) *Mean± SD*	27.7±4.8	30.8± 4.2	33.5± 7.8 ^{A*}
Systolic Blood Pressure (mmHg) *Mean± SD*	111.2±14.5	130.3± 17 ^{A*}	158.1± 18.3 $^{A*, B*}$
Diastolic Blood Pressure (mmHg) *Mean± SD*	82.6± 9.6	82.5± 10 ^{A*}	81.7± 7.7 $^{A*, B*}$
Treatment			
Oral drug	----------	19 (65.6%)	13 (41.9%)
Oral drug + Insulin	----------	10 (34.4%)	18 (58.1%)

*P< 0.05 is significant
A: Significance versus Healthy control
B: Significance versus Controlled diabetes.
(Post hoc tests were used after ANOVA)

Table 2. Glycemic status and Lipid Profile parameters (Mean± SD) in various studied groups.

Parameters	**Healthy Control**	**Controlled DM**	**Uncontrolled DM**
FBG (mg/dl)	88.7 ± 8.3	136 ± 48.6 ^{A*}	187.1 ± 66.1 $^{A*, B*}$
HbA1c (%)	5.4 ± 0.5	6± 0.6	8.1± **0.7** $^{A*, B*}$
Cholesterol (mg/dl)	157.1± 31.2	171.8± 41.2	223.1 ± 41.9 $^{A*, B*}$
TG (mg/dl)	115.2 ± 60	184.7 ± 119 ^{A*}	188.4± 102.1 ^{A*}
HDL (mg/dl)	36.7 ± 8	39.6 ± 10.8	40.3 ± 8.5
LDL (mg/dl)	96.7 ± 26.9	107.7 ± 42.3 ^{A*}	130.8 ± 45 ^{A*}
Atherogenic Index	0.48 ± 0.15	0.61 ± 0.22 ^{A*}	0.65 ± 0.24 ^{A*}

*P< 0.05 is significant
A: Significance versus Healthy control.
B: Significance versus Controlled diabetes
(Post hoc tests were used after ANOVA

Table 3. Levels of Ox-LDL, VCAM-1 and ICAM-1 in the Diabetes compared to Healthy control group:

Parameters	Healthy Patients	Diabetic Patients
Ox-LDL (ng/ml)		
Mean± SD	95.3± 53.2	203.2± 145
Median	80	262
mean rank	18.3	25.7 [A**]
VCAM-1 (ng/ml)		
Mean± SD	201.0± 76.5	391.9± 81.8
Median	340	386.4
mean rank	19.3	31.8 [A*]
ICAM-1 (ng/ml)		
Mean± SD	55.0± 17.4	55.1± 23.1
Median	52.3	61.6
mean rank	26.04	30.6

(Mann-Whitney non parametric test is used to compare mean ranks between groups; *P< 0.05 is significant , **P< 0.01 is highly significant)

Table 4. Levels of Ox-LDL, VCAM-1 and ICAM-1 in the Diabetic groups compared to Healthy control group:

Parameters	Healthy Control	Controlled DM	Uncontrolled DM
Ox-LDL (ng/ml)			
Mean± SD	95.3± 53.2	139.8± 134.7	281.5± 134.7
Median	80	126	326.5
mean rank	18.3	25.7	35.11
Statistics	…….	P: 0.27 [A]	P:0.00 [A**] P:0.001 [B*]
VCAM-1 (ng/ml)			
Mean± SD	201.0± 76.5	372± 84.9	412± 59.4
Median	340	365.6	414.9
mean rank	19.1	28.3	35.1
Statistics	……	P: 0.02 [A*]	P:0.003 [A**] P:0.3 [B]
ICAM-1 (ng/ml)			
Mean± SD	55.0± 17.4	51.2± 5.6	60.5± 24.2
Median	52.3	59.7	69.4
mean rank	25.6	28.5	32.03
Statistics	…….	P:0.56 [A]	P:0.3 [A] P: 0.58 [B]

[A]: Significance versus Healthy control.
[B]: Significance versus Controlled diabetes
(Mann-Whitney non parametric test is used to compare mean ranks between groups; *P< 0.05 is significant , **P< 0.01 is highly significant)

DISCUSSION

Endothelial dysfunction is regarded as an important factor in the pathogenesis of vascular disease in obesity-related type 2 diabetes. The imbalance in repair and injury (hyperglycemia, hypertension, dyslipidemia) results in microvascular changes, ultimately leading to diabetes related complications [5]. Davìet. al [18] reported that endothelial dysfunction associated with lipid modification, lipid accumulation and a pro-inflammatory state complicates the early insulin-resistant diabetic phase.

Our diabetic patients had higher blood pressure than healthy volunteers, with higher values among uncontrolled diabetics. Regarding the lipid profile, TG, LDL and atherogenic index showed significant higher levels among diabetics as a whole compared to healthy control subjects. Moreover, cholesterol levels were significantly higher in uncontrolled diabetics than controlled ones and healthy subjects.

The uncontrolled DM in this study has a significant high BMI than other groups. Kahn et. al. [19] reported that obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance.

Table 5. Correlation coefficient (R) between, and to other investigated parameters

Parameters	Ox-LDL	VCAM-1	ICAM-1
Age	r: 0.358* P: 0.043	r: 0.039 P: 0.81	r:0.06 P:0.6
Systolic blood pressure	r: 0.607** P: 0.001	r: 0.208 P: 0.211	r:0.05 P:0.7
Diastolic blood pressure	r: 0.422* P: 0.023	r: 0.053 P: 0.75	r: 0.1 P:0.5
FBG	r: 0.416** P: 0.008	r: 0.151 P: 0.295	r:0.27* P:0.04
HbA1c	r: 0.384* P: 0.016	r: 0.288* P: 0.047	r:0.24 P:0.07
BMI	r: 0.068 P: 0.72	r: 0.103 P: 0.55	r: 0.09 P: 0.5
Cholesterol	r: 0.126 P:0.43	r: 0.337* P: 0.017	r:0.31* P: 0.03
TG	r: 0.367* P: 0.02	r: 0.144 P: 0.318	r: 0.1 P:0.4
HDL	r: 0.154 P: 0.34	r: 0.236 P: 0.09	r: 0.25 P:0.07
LDL	r: 0.477** P: 0.004	r: 0.103 P: 0.477	r: 0.18 P:0.19
Atherogenic Index	r: 0.32* P: 0.044	r: 0.08 P: 0.55	r: 0.06 P: 0.65
ICAM-1	r: 0.227 P: 0.138	r:0.333** P:0.012	…….
VCAM-1	r: 0.338* P: 0.025	…….	…….

*P< 0.05 is significant
**P< 0.01 is highly significant

Development of early stage atherosclerosis involves the activation of endothelial cells by oxidized low-density lipoprotein (oxLDL) with subsequent increases in endothelial permeability and expression of adhesion molecules favoring the adherence of monocytes to the endothelium [20]. Various scavenger receptors have been recognized in the past two decades that mediate uptake of ox-LDL leading to formation of foam cells, which promotes inflammatory and thrombotic processes [9, 21].

Our data showed increase levels of both LDL and ox-LDL among diabetic patients than healthy controls. It has become abundantly clear over the last decade that the oxidatively modified form of LDL (ox-LDL) is more important than native LDL in atherogenesis [6]. These data goes in accordance with our results which indicates more significant ($p<0.01$) elevation of ox-LDL versus LDL ($p<0.05$) among diabetic patients compared to healthy controls, moreover only ox-LDL was more profound in uncontrolled DM compared to the controlled ones.

Previous experimental and clinical studies reported that oxidative stress plays a major role in the pathogenesis and development of complications of both types of DM. However, the exact mechanism by which oxidative stress could contribute to and accelerate the development of complications in diabetic mellitus is only partly known and remains to be clarified. On the one hand, hyperglycemia induces free radicals and impairs the endogenous antioxidant defense system in patients with diabetes [22]. So increased levels of ox-LDL in our diabetic patients could be attributed to oxidative stress accompanying DM.

The downstream mechanism of CVS complications of increased ox-LDL is not yet clear. Chen et al; [23] reported that ox-LDL induced expression of adhesion molecules (P-selectin and ICAM-1) leading to adhesion of monocytes to endothelial cells initiating the atherosclerosis process.

Regarding CAMs investigated in our study, VCAM-1 only showed increased levels within all diabetic patients compared to healthy group while ICAM-1 had no difference between the studied groups. Williams et al. [24] reported that, among the cell adhesion molecules, VCAM-1, was the key selectivity of monocyte recruitment in early atherogenesis, that may explain its significant elevation among diabetic patients. On the other hand, Mulvihill et al; [25] reported that there was no significant difference in levels of soluble ICAM-1 and VCAM-1 between diabetic and non-diabetic patients.

According to the results of the current study, ox-LDL could be considered as a good predictor of complications in higher glycemic status as it presented significantly higher in uncontrolled diabetes than

controlled diabetes (P<0.05). El-Mesallamy et al. [26] reported that increased level of oxidative stress marker increase their downstream effectors adhesion molecules that occur in type 2 DM. Moreover, inflammatory cytokines stimulated by ox-LDL, activate endothelial cells that express cell adhesion molecules [27]. These data support our findings indicating the significant positive correlation between ox-LDL and VCAM, suggesting its propatheregenic role in triggering cell adhesion molecules formation and developing of atherosclerosis.

Our study suggests that high glucose levels tend to raise ox-LDL and hence cell adhesion molecule (VCAM-1), indicated from their significant positive correlation with FBG and HBA1c. Our results might provide ox-LDL as a potential atherogenic marker specially after detecting its positive correlation with blood pressure (systole and diastole) and atherogenic index. Furthermore, the positive correlation detected between ICAM-1 and VCAM-1 in our studied groups might indicate the same mechanism of their production by ox-LDL.

Our results indicate the impairment and correlation of ox-LDL and VCAM-1 in type II DM among Saudi patients from Qassim region. The results support them as sensitive markers in early prediction of atherosclerosis in diabetic complications.

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