



# Association between Adhesive Molecules and Oxidative Stress Markers among Non-Insulin Dependent Diabetic Patients



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## Abstract

**Background:** Non-insulin dependent diabetes (NIDDM) is usually associated with cardiovascular disorders risk factors.

**Objective:** This study aimed to detect the association between adhesive molecules and oxidative stress biomarkers among obese NIDDM patients.

**Material and Methods:** Eighty obese patients with NIDDM (46 males and 34 females). Their age mean was  $47.53 \pm 6.81$  year and their body mass index (BMI) ranged from 31 to 35Kg/m<sup>2</sup> and a control group included eighty healthy volunteers, who were gender and age matched.

**Results:** Non-insulin dependent diabetes patients showed significantly higher Malondialdehyde (MDA), Superoxide dismutase (SOD), Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1) and E-selection in addition to significantly lower values of Glutathione (GSH) and Glutathione peroxidase (GPX) levels in comparison to controls. Serum levels of ICAM-1, VCAM-1 and E-selection showed a direct relationship with serum MDA and SOD. However, serum levels of ICAM-1, VCAM-1 and E-selection showed an inverse relationship with GSH and GPX.

**Conclusion:** Within the limit of there is an association between adhesive molecules and oxidative stress markers among non-insulin dependent diabetic patients.

**Keywords:** Non-insulin dependent diabetes mellitus; Obesity; Adhesive molecules; Oxidative stress

**Abbreviations:** NIDDM: Non-Insulin Dependent Diabetes; BMI: Body Mass Index; MDA: Malondialdehyde; SOD: Superoxide Dismutase; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; GSH: Glutathione; GPX: Glutathione Peroxidase

## Introduction

Globally, about 6% of population is affected with diabetes mellitus and by 2030 its prevalence will reach 552 million patients [1]. Non-insulin dependent diabetes mellitus (NIDDM) is characterized by insulin resistance, failure of different body organs as kidneys, eyes, blood vessels and heart [2] which are induced by different mechanisms which are complex and not fully understood; that include the direct toxic effects of hyperglycemia, systemic inflammation and oxidative stress [3,4].

Diabetes mellitus is usually associated with multiple organ damage as diabetic retinopathy, cardiovascular disorders, renal, gastrointestinal and sexual disorders [5,6], where there is an association between cardiovascular disorders and oxidative stress

that are induced by systemic inflammation, endothelial dysfunction and abnormal coagulation profile [7-10].

Oxidative stress has an important role in pathogenesis of diabetic complications [11-14] as antioxidant defense is poor that is induced by the metabolic disturbances among NIDDM patients [15]. There seems to be imbalance between oxidant and antioxidant systems in NIDDM patients. These patients are considered to be under oxidative stress because of prolonged exposure to hyperglycemia [16].

Non-insulin dependent diabetes mellitus is usually associated with  $\beta$ -cell failure, hyper insulinemia and hyperlipidemia that induce endothelial dysfunction and abnormal inflammatory

markers [17,18]. Insulin has an essential role in regulation of vascular function by stimulation of the vascular cell adhesion molecule (soluble vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular cell adhesion molecule-1 (ICAM-1) and E-selectin on expression of endothelium [19-21].

This study aimed to detect the association between adhesive molecules and oxidative stress biomarkers among obese NIDDM patients.

### Materials and Methods

#### Subjects

Eighty obese patients with T2DM (46 males and 34 females). The mean of their age was 47.53±6.81 year and their body mass index (BMI) ranged from 31 to 35Kg/m<sup>2</sup>, were selected from the out-patient diabetic clinic of the King Abdalziz Teaching Hospital. They were checked for fasting/random glucose levels. Only participants have fasting blood sugar levels more than 5.6mmol/l or random blood sugar level more than 7.8mmol/l (impaired blood sugar) were included in this study and were further checked for type 2 diabetes mellitus as per recent American Diabetes Association criteria i.e. fasting blood sugar ≥7.0 mmol/l or post-prandial blood sugar ≥11.1mmol/l (2-h plasma glucose 11.1mmol/l during an oral glucose tolerance test) and glycosylated hemoglobin (HbA1c%) >6.5% [22]. Exclusion criteria included smokers, kidney insufficiency, congestive heart failure, pregnant female patients, hepatitis and respiratory failure. Also, eighty apparently healthy, medically free, and treatment naive individuals were recruited to serve as non-diabetic control. All participants signed the informed written consent from.

#### Laboratory analysis

**5.2.1.Serum glucose, glycosylated hemoglobin, insulin and insulin resistance tests:** Hitachi 912 Chemistry Analyzer was used to measure serum glucose using hexokinase reagent from Boehringer Mannheim (Indianapolis, IN 46256). However, AviBion human adiponectin (Acprp 30) was used to measure serum levels of adiponectin. While, a cobas immunoassay analyzer (Roche Diagnostics) was used to measure serum insulin. In addition, homeostasis model assessment (HOMA-IR) was used to detect insulin resistance.  $HOMA-IR = \frac{\text{fasting blood glucose (mmol/l)} \times \text{fasting insulin (mIU/ml)}}{22.5}$  [23]. Assessment of glycosylated hemoglobin (HbA1c%) was carried out by quantitative chromatographic spectrophotometric determination of glycohemoglobin in whole blood using a HbA1c kit (Bio-Systems).

**5.2.2.Adhesive molecules measurements:** Biomarkers of endothelial function included adhesion molecules (ICAM-1 and VCAM-1) and soluble E-selectin levels were measured from frozen plasma samples stored at -80 °C. Enzyme-linked immunosorbent assays kits (ELISAs) were used to measure soluble levels of ICAM-1, VCAM-1 and sE-selectin (GE Healthcare Amersham, Biotrak Easy ELISA).

**5.2.3.Measurement of oxidative stress markers and anti-oxidant status:** For all participants serum (from 10mL blood in

plain vial) and plasma (from 5mL blood in EDTA vial) were separated from the sample within 30min of collection and was stored in pyrogen free polypropylene cryotubes at -80 °C until analysis. Oxidative stress was studied by markers of lipid peroxidation included determining plasma levels of malondialdehyde (MDA) was measured by the method as outlined by Esterbauer et al. [24] and were expressed as mmol/L. However, Anti-oxidant status was studied by glutathione (GSH) The reduced GSH level was measured by adopting the method described by Weckbecker & Cory [25], glutathione peroxidase (GPx) and superoxide dismutase (SOD) were estimated according the spectrophotometric method, as described by Masnini [26], which is based on the dismutation of superoxide anion into oxygen and hydrogen peroxide.

#### 5.3 Statistical analysis

Independent t-test was used to compare mean differences between both groups. Statistical analysis of data was performed using SPSS (Chicago, IL, USA) version 17. The degree of correlation oxidative stress markers, adhesive molecules in obese NIDDM patients was detected by Pearson's product moment correlation coefficients (r).

### Results

Eighty obese patients with NIDDM and eighty healthy control subjects were enrolled in our study, there was no significant differences in BMI between both groups, in addition, NIDDM patients showed significantly higher serum insulin, Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index, fasting blood sugar (FBS), postprandial blood sugar (PPS) and glycosylated hemoglobin (HbA1c) levels in comparison to controls (Table 1).

**Table 1:** Baseline characteristics of NIDDM patients and control subjects.

	Mean +SD		Significance
	NIDDM Group	Control Group	
Age (year)	47.53±6.81	48.12±7.33	P>0.05
Gender (M/F)	46/34	48/32	P>0.05
BMI (kg/m <sup>2</sup> )	30.85±3.62	31.24±3.56	P>0.05
Insulin (mU/l)	15.93±3.74*	8.51±2.49	P<0.05
FBS (mg/dl)	185.62±16.88*	90.13±8.55	P<0.05
PPS (mg/dl)	243.75±21.54*	122.98±14.11	P<0.05
HOMA-IR	6.46±1.28*	3.12±1.03	P<0.05
HbA1c (%)	9.12±2.79*	5.94±1.12	P<0.05

BMI: Body Mass Index; FBS: Fasting Blood Sugar; PPS: Postprandial Blood Sugar; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) Index; HbA1c: Glycosylated Hemoglobin;

(\*) indicates a significant difference between the two groups, P<0.05.

Table 2 summarizes the comparison between NIDDM patients and matched controls. Patients with NIDDM showed significantly higher Malondialdehyde (MDA), Superoxide dismutase (SOD), Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1) and E-selectin in addition to significantly lower values of Glutathione (GSH) and Glutathione peroxidase (GPX) levels in comparison to controls (Table 2).

**Table 2:** Mean value and significance of biochemical parameters of type 2 diabetic patients and control subjects.

	Mean +SD		Significance
	Diabetic Group	Control Group	
MDA (nM/mL)	0.29±0.06*	0.13±0.04	P<0.05
GSH (nM/mL)	3.58±0.74*	4.72±0.85	P<0.05
GPX (UI/mL)	2.61±0.42*	3.83±0.56	P<0.05
SOD (UI/mL)	120.33±18.72*	95.91±14.85	P<0.05
ICAM-1 (ng/ml)	97.26±11.51*	78.63±8.11	P<0.05
VCAM-1 (ng/ml)	815.53±47.26*	711.24±35.19	P<0.05
E-selectin (ng/ml)	16.25±3.83*	9.12±2.52	P<0.05

MDA: Malondialdehyde; GSH: Glutathione; GPX: Glutathione Peroxidase; SOD: Superoxide Dismutase; ICAM-1 = Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule;

(\*) indicates a significant difference between the two groups, P<0.05.

Table 3 summarizes the relationship between parameters of oxidative stress and adhesive molecules in NIDDM patients and the healthy control subjects. Serum levels ICAM-1, VCAM-1 and E-selectin showed a direct relationship with MDA and SOD. However, serum levels of ICAM-1, VCAM-1 and E-selectin showed an inverse relationship with GSH and GPX (Table 3).

**Table 3:** Correlation coefficients test value of the studied variables in the NIDDM group.

	ICAM-1 (ng/ml)	VCAM-1 (ng/ml)	E-selectin (ng/ml)
MDA (nM/mL)	0.71*	0.59*	0.61*
GSH (nM/mL)	0.58*	0.64*	0.56*
GPX (UI/mL)	0.73*	0.75*	0.68*
SOD (UI/mL)	0.62*	0.57*	0.72*

MDA: Malondialdehyde; GSH: Glutathione; GPX: Glutathione Peroxidase; SOD: Superoxide Dismutase; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; SC: Spearman's correlation was used \*: P<0.05.

## Discussion

Currently, non-insulin dependent diabetes mellitus is associated with increased DNA damage due to high level of oxidative stress [27-29]. Our study underscores that patients with non-insulin dependent diabetes mellitus had alteration of adhesive molecules and oxidative stress markers, in addition serum levels of ICAM-1, VCAM-1 and E-selectin showed a direct relationship with MDA and SOD. However, serum levels of ICAM-1, VCAM-1 and E-selectin showed an inverse relationship with GSH and GPX.

In the present study VCAM-1, ICAM-1 and E-selectin level were higher in NIDDM patients than the healthy control subjects. Therefore, the results in this study are consistent with Meigs et al. [30] stated that women with NIDDM had endothelial dysfunction [30]. In addition, Thorand et al. [31] believed that endothelial dysfunction has a role in NIDDM pathogenesis [31]. However, level of sE-selectin was independently associated with diabetes mellitus [32,33]. Ferri et al. [34] found that obese subjects had higher concentration of sVCAM-1, sICAM-1, and E-selection than normal body weight subjects [34].

The exact mechanism of endothelial dysfunction associated with T2DM may due to insulin resistance that induces reduction of dihydropterin reductase activity along with depletion of Tetrahydrobiopterin that is an important co-factor for the catalytic activity of Nitrous Oxides (NOS) [35-39]. Moreover, abnormal blood lipids profile is another possible mechanism for endothelial dysfunction induced by insulin resistance in patients with NIDDM [40,41].

In the present study type 2 diabetes patients showed significantly higher MDA and SOD in addition to significantly lower values of GSH and GPX levels in comparison to normal control subjects. Our results agreed with Kumawat et al. [42] stated that GSH significantly reduced and MDA significantly increased in diabetic patients. A similar study by Kavitha et al [43] showed that diabetic patients had increased level of MDA.

## Conclusion

Within the limit of there is an association between adhesive molecules and oxidative stress markers among NIDDM patients.

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