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Research Article

Association between Metabolic Control, Adhesive Molecules and Oxidative Stress Biomarkers in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is usually associated high risk of cardiovascular disorders because of poor glucose control, abnormal level of inflammatory cytokines, endothelial dysfunction and oxidative stress biomarkers.

Objective: This study aimed to investigate the association between metabolic control, adhesive molecules oxidative stress biomarkers in patients with T2DM.

Material and Methods: NinetyT2DM patients were included in this study, the mean age was 49.16 ± 4.78 year and mean body mass index was 33.27 ± 2.91 kg/m^2. In the other hand another ninety non-diabetic subjects not suffering of any disease, were participated in the study as a control group, the mean age was 50.37 ± 5.13 year and mean body mass index was 32.48 ± 3.51 kg/m^2.

Results: The mean values of HbA1C, HOMA-IR, VCAM-1, ICAM-1, E-selectin and MDA were significantly higher in the T2DM study subjects than in non-diabetic control subjects. In addition, the mean values of GPX, GSH and SOD were significantly lower in the T2DM study subjects than in non-diabetic control subjects. However, The HBA1c and HOMA-IR showed a strong direct relationship with ICAM, VCAM, E-selection and MDA and a strong inverse relationship with GPX, GSH and SOD of T2DM study subjects and non-diabetic subjects ($P < 0.05$).

Conclusion: Our results confirm that hyperglycemia in type 2 diabetes patients' leads to an inhibition of antioxidant enzyme activities and elevation in adhesive molecules.

Keywords: Adhesive molecules; Metabolic control; Oxidative stress; Type 2 Diabetes mellitus

Introduction

Diabetes mellitus (DM) is one of the most common health problem, based on the current statistics from the International Diabetes Federation (IDF, Belgium), more than 415 million subjects worldwide were living with DM in 2015, and this number is expected to reach 640 million people by 2040 [1]. However, based on the International Diabetes Federation (IDF), the prevalence of diabetes among Saudi subjects increased from about 10% in 1989 to about 32% in 2009 and the rate of annual increase in DM prevalence is 0.8% among Saudi men and 0.6% among Saudi women [2]. Diabetes mellitus is considered the 5th leading cause that account for 5.2% of all deaths all over the world. Its economic burden is huge that reach 2.5% to 15% of the whole annual health budget [3]. Diabetes mellitus is a metabolic disorder in which the concentration of fasting plasma glucose (FPG) is higher than 125 mg/dl, or in which blood glucose is above 200 mg/dl at any time of day [4].

Type 2 diabetes mellitus accounts for more than 90% of those with diabetes [5]. Diabetes mellitus is characterized with insulin secretion and/or action defect that result in hyperglycemia [6,7], however chronic hyperglycemia may induce multiple organ damage and dysfunction [8]. Both fasting and postprandial hyperglycemia are independently associated with deteriorating endothelial function and atherosclerosis in patients with dyslipidemia and DM. This is likely mediated by increased inflammation, oxidative stress and decreased NO production and is more pronounced when both derangements coexist [9]. Inflammation play important role in atherosclerosis pathogenesis which induce occurrence of cardiovascular events [10].

The crucial step in atherosclerosis is monocyte adhesion to endothelial surface, after its activation and expression of cell adhesion molecules (CAMs), especially intercellular adhesionmolecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). The activation of CAMs is triggered by inflammation, thus inflammation can be a marker of endothelial activation or even a marker of early atherosclerosis [11,12]. On the other hand, high level of oxidative stress and low levels of anti-oxidative protection increase CAMs and lead to accelerated and diffuse atherosclerosis [13,14]. In the presence of hyperglycemia and hyperlipidemia, this process is more pronounced because of easier lipid peroxidation, glycosylation and

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Table 1: Characteristics of the whole study population.

	Mean ± SD		Significance
	T2DM subjects	Non-diabetic subjects	
Age (year)	49.16 ± 4.78	50.37 ± 5.13	P >0.05
Gender (Male/Female)	52/38	54/36	P >0.05
Body mass index (kg/m^2)	33.27 ± 2.91	32.48 ± 3.51	P >0.05
SBP (mm Hg)	129.34 ± 11.35*	116.57± 8.42	P<0.05
DBP (mm Hg)	85.18 ± 5.27*	77.49 ± 4.83	P<0.05
Fasting plasma insulin (U/l)	11.26 ± 3.29*	7.41 ± 2.15	P<0.05
Fasting plasma glucose (mg/dl)	193.14 ± 21.38*	81.65 ± 6.87	P<0.05

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *Significant level (p<0.05).

Table 2: The mean value and the significance values of different parameters in both groups.

	Mean ± SD		Significance
	T2DM subjects	Non-diabetic subjects	
HbA1C (%)	9.21±1.65	4.34±0.63	P<0.05
HOMA-IR (unites)	5.82 ± 2.37*	2.25 ± 0.91	P<0.05
ICAM-1 (ng/ml)	92.67 ± 10.15	79.12 ± 8.34*	P<0.05
VCAM-1(ng /ml)	809.24 ± 37.13	721.61 ± 29.85*	P<0.05
E-selectin (ng/ml)	15.92 ± 3.45	10.26 ± 2.17*	P<0.05
MDA (mmol/L)	27.31 ± 6.28*	19.11 ± 4.85	P<0.05
GPx (units/gHb)	19.24 ± 4.36*	28.27 ± 6.93	P<0.05
SOD (units/mL)	40.61 ± 8.75*	53.49 ± 11.32	P<0.05
GSH (mmol/gHb)	2096.12 ± 154.16*	2488.35 ± 192.74	P<0.05

HBA1c: Glycosylated Hemoglobin; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; MDA: Malondialdehyde; GPx: Glutathione Peroxidase; SOD: Superoxide Dismutase; GSH: Glutathione; * Significant level (p<0.05).

oxidative protein modification [15] and as a result cardiovascular disease is a feared complication of T2DM [16].

The aim of this study was to investigate the association between metabolic control, adhesive molecules oxidative stress biomarkers in patients with T2DM.

Material and Methods

Subjects

NinetyT2DM patients visiting king Abdulaziz University Hospital, Jeddah, Saudi Arabia, were included in this study, the mean age was 49.16 ± 4.78 year and mean body mass index was 33.27 ± 2.91kg/m^2. Initially, a physician at King Abdulaziz University Hospital examined all participants; their medical history was taken to collect information about general condition, physical activity and current medications if any. All subjects with any cardiovascular conditions (those with a known history of uncontrolled hypertension, congenital and rheumatic heart diseases), any pulmonary disease (obstructive or restrictive lung diseases), were excluded from the study. In the other hand ninety non-diabetic subjects not suffering of any disease, were participated in the study as a control group, the mean age was 50.37 ± 5.13 year and mean body mass index was 32.48 ± 3.51kg/m^2. The Ethics Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University, approved this study. All participants signed a written informed consent.

Measurements

The baseline and anthropometric data were collected for all participants at the time of enrollment. Independent assessors who were blinded to group assignment and not involved in the routine treatment of the patients performed clinical evaluations and laboratory analysis. Body mass index (BMI) was calculated on the basis of weight (kilograms) and height (meters), and subjects were classified as normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). In addition, between 07:30 and 09:00, after an overnight fast of 12 h fasting blood sample was drawn. Serum insulin were determined (Roche Diagnostics GmbH, Mannheim, Germany) using commercially available assay kits. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR). HOMA-IR = [fasting blood glucose (mmol/l) - fasting insulin (mIU/ml)]/22.5 [17].

Measurement of oxidative stress markers and anti-oxidant status: For all participants serum (from 10 ml blood in plain vial) and plasma (from 5 ml blood in EDTA vial) were separated from the sample within 30 min of collection and was stored in pyrogen free polypropylene cryo-tubes at (-80 °C) until analysis. Assessment of lipid markers for peroxidation as malondialdehyde (MDA) was determined according to Buege and Aust [18]. However, Anti-oxidant status, glutathione (GSH) that was determined by the method of Beutler and colleagues [19], in the other hand, glutathione peroxidase (GPx) and superoxide dismutase (SOD) were measured by the method of Nishikimi and colleagues [20].

Measurement of biomarkers of endothelial function: Biomarkers of endothelial function includes inter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin that were measured from frozen serum samples stored at −80°C. Enzyme-linked immunosorbent assays (ELISAs) were used to measure soluble levels of E-selectin, ICAM-1 and VCAM-1 (R&D Systems, France).

Statistical analysis

SPSS (Chicago, IL, USA) version 21 was used for statistical analysis of data. Quantitative variables were described as mean ± SD. An independent t-test was used to compare mean values of each parameter among the groups. To observe possible relationships between HBA1c, ICAM, VCAM, E-selection, MDA, GPX, GSH and SOD, Pearson's correlation coefficient (r) was used. All assumptions were carefully appreciated in each model we followed. All variables with p-value less than 0.05 were considered as statistical significance.

Results

Detailed baseline characteristics of the patients with T2DM subjects and non-diabetic subjects control presented in Table 1. There was a significant difference for all characteristics of the obese T2DM subjects *vs.* non-diabetic subjects, except in the age, gender and body mass index (Table 1).

Regarding the biochemical characteristics of the T2DM group and the non-diabetic group, Table 2 shows that T2DM study subjects had a significant higher serum HbA1C, HOMA-IR, VCAM-1, ICAM-

Table 3: Correlation coefficient (r) of HBA1c, HOMA-IR, ICAM, VCAM, E-selectin, MDA, GPX, GSH and SOD of obese T2DM subjects.

Tested parameters	T2DM subjects		Non-diabetic subjects	
	HbA1C (%)	HOMA-IR (unites)	HbA1C (%)	HOMA-IR (unites)
ICAM-1(ng/ml)	0.632**	0.639**	0.527*	0.711**
VCAM-1(ng /ml)	0.513*	0.628**	0.549*	-0.524*
E-selectin(ng/ml)	0.545*	0.713*	0.624**	0.571*
MDA (mmol/L)	0.519*	0.622**	0.531*	0.621**
GPx (units/gHb)	-0.618**	-0.534*	-0.712**	-0.542*
SOD (units/mL)	-0.521*	-0.662**	-0.573*	-0.729**
GSH (mmol/gHb)	-0.647**	-0.616**	-0.551*	-0.532*

Spearman's correlation was used *: P<0.05 **: P<0.01

1, E-selectin and MDA levels than non-diabetic subjects. However, T2DM study subjects had a significant lower serum GPX, GSH and SOD levels than non-diabetic subjects (P<0.05).

The HBA1c and HOMA-IR showed a strong direct relationship with ICAM, VCAM, E-selectin and MDA and a strong inverse relationship with GPX, GSH and SOD of T2DM study subjects and non-diabetic subjects (Table 3) (P<0.05).

Discussion

Endothelial dysfunction and oxidative stress are considered the principal causes of micro and macro-vascular alterations among T2DM [21-23]. This study aimed to investigate the association between metabolic control, adhesive molecules oxidative stress biomarkers in patients with T2DM. Our present investigation added more confirmations to closely link glycemic control with adhesive molecules and enhanced oxidative stress biomarkers in T2DM.

Firstly, regarding the values of adhesive molecules, the present study showed significantly higher values of ICAM-1, VCAM-1 and E-selectin in T2DM group than the non-diabetic control group. In correlation analysis, ICAM-1, VCAM-1 and E-selectin were significantly and directly associated with the HBA1C and HOM-IR. Our findings agreed with several studies reported increased levels of adhesive molecule in T2DM compared with non-diabetic control subjects In addition, Morigi, et al. [24-26]. Found an association between hyperglycemia and VCAM-1, ICAM-1, and E-selectin because of poor glycemic control in T2DM patients [27]. While, Md Isa and colleagues proved that hyperglycemia activates VCAM-1 expression via increased advanced glycation end products (AGEs) production [28]. Similarly, Su and colleagues confirmed that endothelial dysfunction is present even in early stages of diabetes as they found strong inverse relationship between flow-mediated endothelial dilatation and hyperglycemia in subjects with impaired glucose tolerance and impaired fasting glycemia that indicates endothelial damage due to hyperglycemia Moreover, Motawi, et al. [29] reported that poor glucose control is associated with high VCAM-1 and low GSH levels, in the other hand good glucose control correct these abnormalities for patients with T2DM In contrary, Boulbou, et al. [30]. Stated that there was no change in VCAM-1 levels in patients with T2DM relative to healthy control [31]. This discrepancy between our results and Boulbou, et al. may be due to procedural differences in ethnic groups, glycemic control, and patient's baseline criteria.

Secondly, this study found an increase in the MDA level in patients with type 2 diabetes compared with non-diabetes subjects, supporting findings by other studies [32-34]. As an aldehydic product of lipid peroxidation, MDA is a biomarker of intensified lipid peroxidation and also indirect evidence of high free radical production in diabetes Similarly, Bhutia, et al. [35]. Noted significant increases of MDA level and fasting plasma glucose in poorly controlled T2DM In addition, Nour Eldin, et al. [36] and Volpe, et al. [37,38]. Reported that MDA level was significantly greater in impaired glucose tolerance and T2DM and groups relative to non-diabetic control group.

We observed in blood serum of type 2 diabetes patients a significant decrease of reduced levels of GSH, GPx and SOD as compared with the control subjects. The main function of antioxidant enzymes is to protect cells against different hydroperoxides resulting from reactive ROS through scavenging reactions [39]. The depletion of GSH levels is in agreement with other studies [40-44]. However, Moussa stated that there was an association between GSH depletion and hyperglycemia [32]. The possible mechanism for reduction of GSH as hyperglycemia state indirectly cause depletion of GSH as glucose is favorably by many pathways include increased activity of sorbitol pathway that reduced production of NADPH which necessary for maintenance of GSH in normal level [45,46]. Another possible cause for low level of GSH in T2DM may be the reduced amino acids level that is essential for GSH synthesis [47,48]. However, the reduction of the GPx activity in type 2 diabetes patients has been proved by Niedowicz and Daleke [41] and Rahbani-Nobar, et al. [49]. The levels of GPx were significantly decreased in T2DM, this decrease may be due to protein glycation, which is a mechanism that damages the protein within antioxidant enzymes [50]. While, Gillery stated that hyperglycemia generates an increase of the intensity of the reactions of nonenzymatic glycation proteins that are associated with oxidative stress in diabetic patients [51].

Finally, we observed a significant correlation between the degree of glycemic control (HBA1C and HOMA-IR) and severity of oxidative stress, these findings are compatible with Soliman that correlated HBA1C with GSH and SOD levels [52], and with those of Kassim that associated HBA1C with MDA and SOD levels However, Goodarzi, et al. [53]. Support the correlation between oxidative stress and the degree of hyperglycemia [54]. In contrast to the findings of the present study, no correlation was found by Rahbani-Nobar, et al. Who have correlated HBA1C with SOD and GPx levels in type 2 diabetes patients [49].

Conclusion

Our results confirm that hyperglycemia in type 2 diabetes patients leads to an inhibition of antioxidant enzyme activities (GSH, GPx and SOD), elevation in MDA activity and higher values of adhesive molecules (ICAM-1, VCAM-1 and E-selectin). Therefore, hypoglycemia treatment has probably favorable effect on the antioxidant system and endothelial function in T2DM.

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