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Relationships between Systemic Inflammation, Oxidative Stress, Endothelial Dysfunction Molecules and Glycemic Control in Non-Insulin Dependent Diabetes

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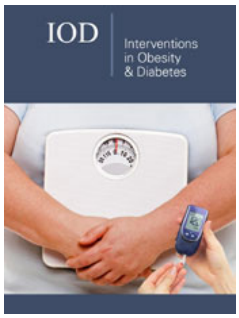

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Abstract

Background: Non-insulin dependent diabetes (NIDDM) usually had high risk for vascular dysfunction.

Objective: The target of this study is to measure the relationships between systemic inflammation, oxidative stress and glycemic control in non-insulin dependent diabetes.

Material and Methods: Ninety obese patients with NIDDM (54 males and 36 females). Their age mean was 49.13±5.25 year, their body mass index (BMI) ranged from 31 to 36Kg/m^2, and a control group included Nighty healthy volunteers, who was gender and age matched.

Results: Our study results underscores that NIDDM patients had higher significant values of Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index, glycosylated hemoglobin(HBA1c), Malondialdehyde (MDA), Superoxide dismutase (SOD), Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1), E-selectin, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) in addition to lower significant values of the quantitative insulin-sensitivity check index (QUICKI), Glutathione (GSH) and Glutathione peroxidase (GPX) levels in comparison to controls., in addition serum levels of ICAM-1, VCAM-1, E-selectin MDA ,SOD, CRP, TNF-α and IL-6 showed a direct relationship with HOMA-IR and HBA1c. However, serum levels of GSH and GPX showed an inverse relationship with HOMA-IR and HBA1c. However, serum levels of ICAM-1, VCAM-1, E-selectin MDA, SOD, CRP, TNF-α and IL-6 showed an inverse relationship with QUICKI. However, serum levels of GSH and GPX showed a direct relationship with QUICKI.

Conclusion: There is an association between increased systemic inflammation, oxidative stress, endothelial dysfunction molecules and poor metabolic control in NIDDM.

Keywords: Endothelial dysfunction molecules; Cytokines; Metabolic control; Non-insulin dependent diabetes mellitus; Obesity; Oxidative stress

Abbreviations: NIDDM: Non-Insulin Dependent Diabetes Mellitus; BMI: Body Mass Index; QUICKI: Quantitative Insulin-Sensitivity Check Index; SOD: Superoxide Dismutase

Introduction

Diabetes mellitus affects about 6% of population where globally more than 550 million subject will have diabetes by 2030 [1]. However, non-insulin dependent diabetes mellitus (NIDDM) through different mechanisms include lack of metabolic control, oxidative stress and inflammatory cytokines induce dysfunction of different body systems as kidney, heart, blood vessels and eye [2,3]. Diabetic complications are related to abnormal levels of oxidative stress biomarkers induced by poor metabolic control [4-8]. Poor control of blood glucose level may induce abnormal levels of oxidative stress biomarkers [9]. β-cell failure, hyperinsulinemia and hyperlipidemia among NIDDM patients induce endothelial dysfunction and abnormal inflammatory markers [10-14]. Low-grade systemic inflammation is involved in the pathogenesis of NIDDM [15] that abnormal level of inflammatory cytokines may impair glucose control and induce insulin resistance [16-20]. Activation of systemic inflammation adversely affects the insulin action that lead to increased pro-inflammatory cytokines expression [21] that in turn induce more inflammatory response and insulin resistance

exacerbation [22]. The objective of this study is to measure the relationships between systemic inflammation, oxidative stress and metabolic control in NIDDM.

Materials and Methods

Subjects

Ninety obese patients with NIDDM, the mean of their age ranged from 40-55 years and their body mass index (BMI) ranged from 30 to 35Kg/m^2. Smokers and patients with renal insufficiency, congestive heart failure, pregnancy, respiratory failure and hepatitis were excluded. In addition to nighty healthy non-diabetic subjects participated in this study as a control group who was gender and age matched. Before sharing in this study, informed written consent from was signed by all participants.

Laboratory analysis

Glucose control measurement: Hitachi 912 Chemistry Analyzer will be used to measure serum glucose. However, cobas immunoassay analyzer (Roche Diagnostics) will be used to measure serum insulin. Homeostasis model assessment (HOMA-IR)=[fasting blood glucose (mmol/l)_fasting insulin (mIU/ml)]/22.5 is the formula that will be used to calculate the insulin resistance [2]. While the quantitative insulin-sensitivity check index (QUICKI) assessed by the formula: QUICKI=1/[log(insulin) + log(glucose)] is the formula that was used to calculate insulin sensitivity [23].

Inflammatory cytokines measurements: TNF-α and IL-6 were measured using GE Healthcare Amersham, Biotrak Easy ELISA). While enzymatic-colorimetric method with kits (Roche Diagnostics, Mannheim, Germany) were used to measure C-reactive protein (CRP).

Measurement of oxidative stress status: Method of Buege and Aust is the procedure was used to measure malondialdehyde (MDA) and conjugated dienes (CD) as measures for oxidative stress status [24]. However, method of Beutler and colleagues is the procedure was used to measure anti-oxidant status, glutathione (GSH) [25], method of Nishikimi and colleagues is the procedure used to measure glutathione peroxidase (GPx) and superoxide dismutase (SOD) [26].

Statistical analysis

The mean values of the investigated parameters were detected at the beginning and at the end of the study for both groups and they were compared by student paired "t" test. While the unpaired" test was used to compare between the two groups. Pearson or Spearman rank correlation was used to detect the relationship between the investigated parameters (P<0.05).

Results

Baseline data proved no significant differences in the mean values of age and BMI between both groups. While parameters of metabolic control included serum insulin, fasting blood sugar (FBS) and postprandial blood sugar (PPS) levels were higher among NIDDM patients than control subjects (Table 1). Our study results underscores that NIDDM patients had higher significant values of HOMA-IR, HBA1c, MDA, SOD, ICAM-1, VCAM-1, E-selectin, CRP, TNF-α and IL-6 in addition to lower significant values of QUICKI, GSH and GPX levels in comparison to control subjects. Table 2 shows the relationship between parameters of NIDDM patients and the control subjects. Serum levels of GSH and GPX showed an inverse relationship with HOMA-IR and HBA1c. While, serum levels of ICAM-1, VCAM-1, E-selectin MDA, SOD, CRP, TNF-α and IL-6 showed an inverse relationship with QUICKI. However, serum levels of GSH and GPX showed a direct relationship with QUICKI (Table 3).

Table 1: Baseline criteria of all participants.

	Mean+SD		Significance
	NIDDM Group	Control Group	
Age (year)	49.13±4.25	48.78±5.11	P>0.05
Gender (M/F)	54/36	57/33	P>0.05
BMI (kg/m^2)	32.23±3.47	31.89±3.12	P>0.05
Insulin (mU/l)	14.74±2.26*	9.54±1.85	P<0.05
FBS (mg/dl)	182.31±15.22*	89.25±6.92	P<0.05
PPS (mg/dl)	238.57±29.14*	121.24±13.53	P<0.05

(*)=P<0.05.

Table 2: Mean value and significance of biochemical parameters of NIIDM and control groups.

	Mean+SD		Significance
	NIDDM Group	Control Group	
MDA (nM/mL)	0.27±0.05*	0.16±0.03	P<0.05
GSH (nM/mL)	3.41±0.63*	4.85±0.89	P<0.05
GPX (UI/mL)	2.61±0.74*	3.94±0.85	P<0.05
SOD (UI/mL)	117.26±21.15*	97.22±13.26	P<0.05
ICAM-1 (ng/ml)	98.14±9.27*	76.46±7.21	P<0.05
VCAM-1 (ng /ml)	831.28±43.16*	723.42±37.29	P<0.05
E-selectin (ng/ml)	13.75±1.93*	9.21±1.68	P<0.05
CRP(mg/dl)	14.66±2.68*	9.17±1.86	P<0.05
TNF-α (pg/mL)	5.85±1.55*	3.94±1.47	P<0.05
IL-6 (pg/mL)	7.34±1.93*	5.46±1.52	P<0.05
HOMA-IR	6.85±1.24*	4.13±1.13	P<0.05
HBA1c	7.96±1.47*	6.11±0.92	P<0.05
QUICKI	0.121±0.016*	0.183±0.025	P<0.05

(*)=P<0.05.

Table 3: Relationship between parameters of NIDDM patients and the control subjects.

	QUICKI	HOMA-IR	HBA1c
MDA (nM/mL)	-0.563**	0.682***	0.595**
GSH (nM/mL)	0.671***	-0.526**	-0.567**
GPX (UI/mL)	0.621**	-0.668***	-0.679***
SOD (UI/mL)	-0.435*	0.519**	0.488*
ICAM-1 (ng/ml)	-0.516**	0.643***	0.571**

ICAM-1 (ng/ml)	-0.618***	0.523**	0.539**
E-selectin (ng/ml)	-0.627**	0.474*	0.681***
CRP(mg/dl)	-0.484*	0.522**	0.514**
TNF-α (pg/mL)	-0.657***	0.673***	0.441*
IL-6 (pg/mL)	-0.491*	0.587**	0.682***

*: P<0.05, **: P<0.01, ***: P<0.001

Discussion

Oxidative stress induces DNA damage in NIDDM [27-30], in addition risk of cardiovascular complications are 2-4 times than non-diabetics [31-33]. Our study underscores that patients with NIDDM had alteration of cytokines, endothelial dysfunction markers and oxidative stress markers, also serum levels of ICAM-1, VCAM-1, E-selectin MDA, SOD, CRP, TNF-α and IL-6 showed a direct relationship with HOMA-IR and HBA1c. However, serum levels of GSH and GPX showed an inverse relationship with HOMA-IR and HBA1c. Moreover, serum levels of ICAM-1, VCAM-1, E-selectin MDA, SOD, CRP, TNF-α and IL-6 showed an inverse relationship with QUICKI. However, serum levels of GSH and GPX showed a direct relationship with QUICKI. Several previous studies focused on proving an association between development of insulin resistance and type 2 diabetes [18] and oxidative biomarkers [34,35], inflammatory cytokines [36-38] and endothelial function biomarkers [39-41]. Regarding values of endothelial dysfunction, NIDDM patients had a higher mean values of VCAM-1, ICAM-1 and E-selectin level than control subjects. These findings consistent with Meigs, et al. [39,42] reported that NIDDM patients had endothelial dysfunction [39,42-44]. Moreover, Ferri et al. [45] stated that VCAM-1, ICAM-1, and E-selectin levels were higher among obese subjects than normal subjects [45]. Insulin resistance dyslipidemia were the exact endothelial dysfunction mechanism associated with NIDDM [46].

In the present study, the mean values of MDA and SOD was higher, where the mean values of GSH and GPX was lower among NIDDM patients than normal control subjects. These findings confirmed by Kumawat et al. [47] mentioned that GSH significantly lower and MDA significantly higher among diabetic subjects [47]. Moreover, Kavitha et al. [48] reported that diabetics had higher MDA level [48]. Regarding the inflammatory cytokines, the present study NIDDM patients had significantly higher CRP, TNF-α and IL-6 levels in comparison to normal control subjects. Many studies proved the relation between inflammation and T2DM future development [49,50]. While Liu et al. [51] conducted a meta-analysis included 19 previous studies and proved the link between T2DM and systemic inflammation [51]. Similarly, Julia et al. [52] proved that association between onset of T2DM and endothelial dysfunction & cytokines [52]. Moreover, de Souza Bastos [53] proved that dyslipidemia in T2DM associated with systemic inflammation and oxidative stress [53]. The association between increased systemic inflammation, oxidative stress, endothelial dysfunction molecules and poor metabolic control in NIDDM may be linked to the inactivation of the anti-aging gene Sirtuin 1 that is critical insulin resistance and systemic inflammation. Sirtuin 1 inactivation will lead to loss of metabolic control, increased oxidative stress and inflammatory cytokines dysfunction that lead to multiple organ disease such as diseases of the kidney, liver, heart, brain, blood vessels and eye [54,55]. The possible mechanism that relate insulin resistance to systemic inflammation is complex that may be related to involve increased effect of over produced oxidative stress on the mitochondrial function and endoplasmic reticulum in target tissues [56].

Conclusion

There is an association between increased systemic inflammation, oxidative stress, endothelial dysfunction molecules and poor metabolic control in NIDDM.

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