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Association between Oxidative Stress, Systemic Inflammation and Renal Function in Type 2 Diabetic Nephropathy

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Abstract

Background: Diabetic nephropathy (DN) is the common microvascular diabetic complication worldwide. However, there is still insufficient understanding of the full mechanism related to progressive diabetic renal disease. Objective: This study aimed to detect the association between oxidative stress, systemic inflammation and kidney function in patients with type 2 diabetic nephropathy.

Material and Methods: One hundred-twenty obese T2DM patients (72 males and 48 females), their body mass index (BMI) was 31-36 Kg/m^2 and the mean of diabetes chronicity was 12.65±2.49 years enrolled in the present study in addition to sixty apparently healthy individuals were recruited to serve as non-diabetic control. Participants were included three groups; seventy-five subjects with diabetic nephropathy (group I), 45 diabetic subjects without nephropathy (group II) and 60 controls (group III).

Results: The mean values of the biochemical parameters of the three groups proved that both group (I) and group (II) had a significant higher serum creatinine, TNF-α, IL-6, CRP and MDA levels than group (III) in addition to a significant lower serum GPX, GSH and SOD levels in group (III) than both group (I) and group (II). However, there were significant differences in all biochemical characteristics between group (I) and group (II). Moreover, the values of IL-6, TNF-α, CRP and MDA showed a strong direct relationship with value of creatinine in the three groups. However, the values of GPX, GSH and SOD showed a strong inverse relationship with value of creatinine in the three groups ($P<0.05$).

Conclusion: There is an evidence that oxidative stress and inflammatory cytokines appear to be significantly correlated with renal function among patients with diabetic nephropathy.

Keywords: Inflammatory cytokines; Diabetic nephropathy; Oxidative stress

Introduction

Diabetic nephropathy (DN) is a metabolic disorder with high rate of morbidity and mortality. Global pattern of diabetic nephropathy incidence is not entirely explored, but its incidence has already occurred widely and is estimated to be increased in prevalence [1]. However, DN is one of the main microvascular diabetic complications that leads to renal failure worldwide [2-5]. While, DN occur in 20-40% of type 2 diabetes mellitus (T2DM) patients and the principal etiology of renal failure [6,7].

Patients with DN suffer from high rate of morbidity and mortality. In fact, a rapid kidney function decline is a predictor for both cardiovascular disorders as well as all-cause mortality [8-10]. Risk factors of DN include poor metabolic control, diabetes duration, race, heredity, life style, diet composition, aging and hypertension. On the other hand, oxidative stress and inflammatory factors are 2 serious elements in promoting DN [11,12].

Hyperglycemia induces oxidative stress and inflammation [13]. In addition, poor glycemic control induce abnormal level of oxidative stress markers [14,15]. In the other hand, oxidative stress induce dysfunction of β-cell that lead to insulin resistance development, diabetes and its associated microvascular complications [16-21], so that patients with T2DM are under oxidative stress because of prolonged exposure to hyperglycemia [22].

Researches proved that hyperglycemia that induced oxidative stress and inflammation may play vital role in the pathogenesis of DN [23,24]. Hyperglycemia in diabetic patients leads to mitochondrial dysfunction, advanced glycation end processes and other factors, and generate the reactive free radicals, then triggers the DNA fragmentation that lead to cell death [25]. Hyperglycemia also causes oxidative stress, decreases the regeneration of glutathione (GSH) from oxidized GSH and reduces the availability of nicotinamide adenine dinucleotide phosphate [26,27]. This study aimed to detect the association between oxidative stress, systemic inflammation and kidney function in patients with type 2 diabetic nephropathy.

Materials and Methods

Subjects

One hundred-twenty obese T2DM patients (72 males and 48 females), their body mass index (BMI) was 30 to 36 Kg/m^2 and the mean of diabetes chronicity was 12.65±2.49 years were selected from the out-patient diabetic clinic of the King Abdalziz Teaching Hospital. Exclusion criteria included smokers, kidney insufficiency, congestive heart failure, pregnant female patients, hepatitis and respiratory failure. In addition, sixty apparently healthy, medically free, and treatment naive individuals were recruited to serve as non-diabetic control. Participants were included three groups; seventy-five diabetic nephropathy patients (group I), 45 diabetic patients without nephropathy (group II) and 60 controls (group III). The Ethics Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University, approved this study.

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. Triglycerides, high-density lipoprotein cholesterol (HDL^{-c}) and plasma glucose concentration were determined (Roche Diagnostics GmbH, Mannheim, Germany) using commercially available assay kits. Glycated hemoglobin (HbA1c) was measured using a kit obtained from BioSystems (Spain). Serum creatinine was measured with a kit obtained from Stanbio Laboratory (USA).

A. 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 (-80ºC) until analysis. Assessment of lipid markers for peroxidation as malondialdehyde (MDA) were determined according to Buege and Aust. [28]. However, Anti-oxidant status, glutathione (GSH) that was determined by the method of Beutler and colleagues [29], in the other hand, glutathione peroxidase (GPx) and superoxide dismutase (SOD) were measured by the method of Nishikimi and colleagues [30].

B. Measurement of inflammatory cytokines: Venous blood samples after a 12-hours fasting were centrifuged at 4 °C (1000Xg for 10 min). "Immulite 2000" immune-assay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA) analyzed IL-6 level. However, TNF-α and CRP levels were measured by ELISA kits (R&D, USA) by using ELISA technique (ELX 808; Bio-Tek Instruments, USA).

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 creatinine and TNF-α, IL-6, CRP, 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

Table 1: Characteristics of the whole study population.

	Mean±SD		
	Group (1)	Group (2)	Group (3)
Age (year)	47.18±4.97	46.35±5.24	49.13±4.28
Gender (Male/ Female)	36/28	31/25	33/27
Body mass index (kg/m^2)	32.66±2.49	32.14±3.12	31.95±2.63
SBP (mm Hg)	122.57±14.18	120.32±12.83	118.71±10.17
DBP (mm Hg)	80.22±5.42	77.38±6.14	75.23±5.68
Total cholesterol (mg/dl)	262.64±38.21^{a,b}	253.53±34.79^{c}	187.24±21.37
Triglyceride (mg/dl)	242.67±35.92^{a,b}	221.56±31.43c	173.13±27.54
HDL-c (mg/dl)	33.98±5.25^{a,b}	35.77±5.32^{c}	41.87±7.16
LDL-c (mg/dl)	175.31±28.12^{a,b}	171.92±26.34^{c}	102.50±14.11
Fasting plasma glucose (mg/dl)	263.74±34.78^{a,b}	165.13±22.51^{c}	84.19±9.13
HbA1C (%)	8.96 ±1.53^{a,b}	7.45 ±1.36^{c}	4.23±0.72

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; HDL-c: High-density lipoprotein cholesterol; LDL^{-c}: Low-

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density lipoprotein cholesterol; HBA1c: glycosylated hemoglobin; a P <0.05 : group (1) compared with group (2); b P<0.05 : group (1) compared with group (3); c P < 0.05 : group (2) compared with group (3); *Significant level (p<0.05).

Detailed baseline characteristics of the participants of the three groups presented in Table 1. There was a significant difference for all characteristics of type 2 diabetic patients with nephropathy (group 1) and both type 2 diabetic patient without nephropathy (group 2) and the non-diabetic patients (group 3), except in the age, gender, body mass index, systolic blood pressure and diastolic blood pressure (Table 1).

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

	Mean ±SD		
	Group (1)	**Group (2)**	**Group (3)**
TNF- α (pg/mL)	11.92±2.36*	10.14±2.13	8.67±1.85
IL-6 (pg/mL)	6.23±1.71*	4.55±1.24	3.84±1.18
CRP (mg/L)	4.98± 1.42*	3.21±1.38	2.45±1.17
Creatinine (µmol/mol)	87.52±13.25	81.36±11.19	70.27±8.46
MDA (mmol/L)	26.74±6.13*	22.23±5.21	18.89±4.52
GPx (units/gHb)	20.14±4.26*	23.87±5.12	28.13±7.25
SOD (units/mL)	39.28±8.95*	45.36±10.31	54.29±11.76
GSH (mmol/gHb)	2103.27±164.32*	2315.94±188.45	2526.35±197.11

TNF-α: tumor necrosis factor – alpha; IL-6: Interleukin-6; CRP: C-Reactive Protein; CD: Conjugated Dienes; MDA: Malondialdehyde; Gpx: Glutathione Peroxidase; SOD: Superoxide Dismutase; GSH: Glutathione; A P< 0.05 : Group (1) Compared With Group (2); B P <0.05 : Group (1) Compared With Group (3); C P<0.05 : Group (2) Compared With Group (3); *Significant Level (P<0.05).

Regarding the biochemical characteristics of the three groups, Table 2 shows that both group (1) and group (2) had a significant higher serum creatinine, TNF-α, IL-6, CRP and MDA levels than group (3) in addition to a significant lower serum GPX, GSH and SOD levels in group (3) than both group (1) and group (2). However, there were significant differences in all biochemical characteristics between group (1) and group (2) (P<0.05).

The values of IL-6, TNF-α, CRP and MDA showed a strong direct relationship with value of creatinine in the three groups. However, the values of GPX, GSH and SOD showed a strong inverse relationship with value of creatinine in the three groups (Table 3) (P<0.05).

Table 3: Correlation coefficient (r) of IL-6, TNF-α, CRP, MDA, GPX, GSH and SOD of the three groups. Spearman's correlation was used *: P<0.05 **: P<0.01

Tested parameters	Group (1)	Group (2)	Group (3)
TNF- α (pg/mL)	0.614**	0.528*	0.592**
IL-6 (pg/mL)	0.637**	0.615**	0.552*
CRP (mg/L)	0.513*	0.563*	0.617**
MDA (mmol/L)	0.522*	0.514*	0.531*
GPx (units/gHb)	-0.673**	-0.634**	-0.569*
SOD (units/mL)	-0.611**	-0.529*	-0.517*
GSH (mmol/gHb)	-0.524*	-0.551*	-0.647**

Discussion

Diabetic nephropathy (DN) considered as the most serious diabetic complication; while renal replacement is required for the majority of subjects with chronic renal disease among patients with T2DM [31,32], where poor glycemic control [33] is related to abnormal oxidative stress and systemic inflammation that induce progressive diabetic renal lesion [34-36]. Therefore, the purpose of this study was to investigate the association between oxidative stress, inflammatory cytokines and kidney function in patients with type 2 diabetic nephropathy.

The principal finding of our study indicated that creatinine, inflammatory cytokines and oxidative stress markers were significantly higher in T2DM with DN and T2DM without DN than the non-diabetic control subjects. These results agreed with researchers conducted by Sekizuka et al., Suzuki et al. & Choudhary et al. [37-39] showed that serum IL-6 levels increased in type 2 diabetic nephropathy patients compared with diabetic patients without nephropathy. Similar result also found by Shelbaya et al. involved 50 subjects, consisted of 40 patients with type I diabetes and 10 normal subjects [40]. The research found that serum IL-6 levels and CRP were significantly higher in type 1 diabetics. However, Navarro et al. found an increase in the gene expression for pro-inflammatory cytokine in patients with DN [41]. Several studies reported that TNF-α levels increased along with progressivity of DN. It indicates that there is an association between the increase of TNF-α levels and the incidence & the course of renal lesion among diabetics [42-44]. Moreover, El Mesallamy et al. [45] reported that among 65 type 2 diabetic subjects and 17 control, there was a significant elevation in inflammatory cytokines in T2DM with DN as compared with control and normo-albuminuric subjects [45]. However, Navarro

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et al. & Moriwaki et al. [46,47] reported an association between progression of DN and urinary TNF-α excretion.

Regarding the oxidative stress markers, several reports stated that there was reduced level of GSH in diabetes associated with systemic inflammation [40-50]. In addition, in β-cell dysfunction may be related to abnormal GSH level which has a role in the incidence of long-term diabetic complications [51]. Moreover, low GSH is related to DNA oxidative damage in T2DM [52]. Many studies reported decline in the level of SOD in diabetic tissue and blood [53-56]. While, study performed by Lucchesi and colleagues to observe the oxidative balance of diabetic rats reported diminished activity of SOD and other antioxidative enzymes in the liver tissue [57]. In the other hand, several studies reported an increased MDA level in patients with T2DM [58,59]. In addition, Baynes & Ramesh et al. [60,61] reported that lipid peroxidation in diabetes induced many secondary chronic complications including atherosclerosis and neural disorders. While, Yang et al. [62] found greater serum lipid peroxidation evaluated in terms of MDA in hyperglycemic mice and proposed that the increase in lipid peroxidation exacerbated the occurrence of myocardial infraction through NADPH oxidase activation.

Finally, in our study, there was a strong direct relationship between values of inflammatory cytokines and oxidative stress markers with value of creatinine in the three groups. However, the values of anti-oxidative stress markers showed a strong inverse relationship with value of creatinine in the three groups. Our results consistent with the studies of Chen et al., Shikano et al. & Kafle et al. [63-65]who confirmed the possible role of IL-6 and TNF-α and Gpx in diabetic renal damage progress. While, Xu et al. [66] conducted a cohort study on 176 patients with chronic kidney disease and 67 healthy controls and reported increased level of CRP, IL-6 and MDA in addition to decreased levels of SOD and GSH-PX (glutathione peroxidase) along with inverse relationship between estimated glomerular filtration rate (eGFR) and MDA associated with positive relationship with SOD and GSH-PX among patients with chronic kidney disease (CKD). Moreover, Aslan et al. [67] reported significant correlations between oxidative stress and microalbuminuria levels in patients with DS. However, Sreeram et al. [68] reported that among 108 CKD patients, as the renal damage progressed the values of MDA & CRP increased while the values of GPx and SOD decreased.

Conclusion

The current study provides evidence that oxidative stress and inflammatory cytokines appear to be significantly correlated with renal function among patients with diabetic nephropathy.

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