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Serum Extracellular Superoxide Dismutase Concentration in Type 2 Diabetic Patients with Nephropathy: An Investigation of the Relationship

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Abstract

Objective: Diabetic nephropathy (DN) is a leading cause of end-stage renal disease and is characterized by complex pathogenic mechanisms involving oxidative stress. Antioxidant enzymes play a crucial role in combating oxidative stress and potentially slowing down the progression of DN. Extracellular superoxide dismutase (EcSOD) is an important enzyme located in the extracellular spaces that scavenges the superoxide anion, a key contributor to oxidative stress.

Methods: In this study, we enrolled a total of 167 diabetic patients, with 101 patients without nephropathy serving as the control group. The DN group consisted of 66 patients, who were further categorized into subgroups based on their albumin creatinine ratio (ACR): microalbuminuria (ACR 30-300 mg/g) and macroalbuminuria (ACR > 300 mg/g). EcSOD enzyme concentrations were measured using the Enzyme-Linked Immuno-Sorbent Assay (ELISA) technique.

Results: The mean EcSOD concentration in the DN group was 166.18 ng/mL (±66.02), slightly higher than the diabetic-only group (157.68 ng/mL ±66.67), but this difference was not statistically significant (P value = 0.420). Within the DN group, the microalbuminuria subgroup exhibited an EcSOD concentration of 166.95 ng/mL (±68.83), while the macroalbuminuria subgroup showed a concentration of 159.73 ng/mL (±36.96). However, the comparison between these subgroups did not yield a statistically significant difference (P = 0.787).

Conclusions: Based on our findings, the concentration of EcSOD does not appear to be significantly associated with the development of nephropathy in Type 2 diabetic patients. Further investigations are warranted to explore other potential mechanisms contributing to the pathogenesis of diabetic nephropathy and to determine the role of EcSOD in this context.

Keywords: Extracellular Super Oxide Dismutase, SOD3, Diabetic Nephropathy, Oxidative Stress.

Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent global health concern and is associated with significant morbidity and mortality [1]. Both microvascular and macrovascular complications are commonly observed in individuals with Type 2 diabetes [2]. Among these complications, diabetic nephropathy (DN) stands out as a serious microvascular complication of diabetes mellitus [1]. The incidence of DN is steadily rising worldwide, and it represents a leading cause of chronic kidney disease and end-stage renal failure [3].

The pathophysiology of DN involves a complex interplay of inflammatory, hemodynamic, and metabolic pathways, ultimately leading to proteinuria, reduced glomerular filtration rate, and eventual renal failure [4]. Notably, the kidney is a metabolically active organ, rendering it susceptible to oxidative stress [5]. Mitochondrial electron transport chain-mediated overproduction of superoxide plays a central role in the development of diabetic complications, including DN [6].

Oxidative stress (OS) arises from an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense system within the body [7]. Antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, play a critical role in maintaining the delicate balance of these metabolites at low levels in tissues [8].

Superoxide dismutase (SOD) is an enzyme that facilitates the dismutation of the superoxide anion, a prominent ROS molecule, into hydrogen peroxide [9]. Among the SOD isozymes, extracellular superoxide dismutase (EcSOD), also known as SOD3, is unique in its localization within the extracellular matrix and at cell surfaces [10].

Experimental studies have demonstrated the protective role of EcSOD against oxidative stress in renal tissues [11, 12]. Additionally, several studies have explored the association between EcSOD concentration and the pathogenesis and progression of DN [13]. However, contradictory findings have been reported, with some studies failing to establish a clear correlation between EcSOD concentration and the pathogenicity of DN [14]. Consequently, further extensive research is warranted to definitively elucidate the role of EcSOD in the development of diabetic nephropathy.

Therefore, the objective of this study was to investigate the potential relationship between serum EcSOD concentrations and the early development of diabetic nephropathy in patients with Type 2 diabetes.

Materials and Methods

A case-control study was conducted involving 167 patients with type 2 diabetes, ranging in age from 32 to 73 years. The study was carried out at the Diabetes and Endocrinology Center in Al-Sadr Medical City, Al-Najaf Governorate, which serves as a primary healthcare center for routine examination and treatment of diabetic patients in the region. These patients had been diagnosed and followed up by specialized physicians, and their medical records were available at the center. Based on the presence of nephropathy, the patients were divided into two groups: a control group consisting of 101 patients without nephropathy, and a patient group comprising 66 patients with nephropathy. Nephropathy was defined as a urinary albumin to creatinine ratio (ACR) greater than 30 mg/g. The demographic, physiological characteristics, and medication profiles of both groups were well-matched.

Exclusion criteria were applied, including patients with cardiovascular diseases, liver diseases, cancer, hematuria, infections, recent intense physical exercise, severe disorders, renal diseases unrelated to diabetic nephropathy, individuals undergoing dialysis, those with an estimated glomerular filtration rate (eGFR) less than 15 ml/min/1.73 m2, smokers, and pregnant women.

A comprehensive clinical examination was performed for all participants, including a detailed medical history and biochemical analysis. Relevant information such as sex, age, duration of diabetes, weight, and height was documented.

Blood Sample Collection:

Approximately six milliliters of blood were collected from each participant through peripheral vein puncture. The blood samples were divided into two parts. The first part (5 mL) was placed in a gel tube and allowed to coagulate at 37°C for approximately 15 minutes. Subsequently, the samples were centrifuged at 2000 xg for 10-15 minutes. The resulting sera were then stored at -20°C for later estimation of various parameters. The second part (1 mL) was collected in an EDTA tube and used for HbA1c measurement.

Collection of Urine Samples:

Urine samples from diabetic patients were collected in sterile containers. The samples were separated into two sections: one for albumin determination and the other for creatinine determination.

Measurement of Biomarkers:

The Beckman Coulter AU480 analyzer was employed to measure the serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, urea, creatinine, glucose, and hemoglobin A1c (HbA1c) in accordance with the manufacturer's instructions. Urinary levels of protein and creatinine were measured using spectrophotometry in random spot samples.

The albumin creatinine ratio (ACR) was calculated according to the method proposed by Sumida et al. [15] based on the protein to creatinine ratio and presented in mg/g units.

The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$eGFR = 141 \times \min(Scr/\kappa,1)\alpha \times \max(Scr/\kappa,1)\text{-}1.209 \times (0.993)\,Age \times (1.018 \text{ if female})$$

Where Scr is serum creatinine expressed in mg/dL, $\kappa = 0.9$ mg/dL for males and 0.7 mg/dL for females; $\alpha = -0.411$ for males and -0.329 for females, min refers to the minimum of Scr/ κ or 1, and max refers to the maximum of Scr/ κ or 1 [16].

Sandwich enzyme-linked immunosorbent assay (ELISA) was performed to measure the level of extracellular superoxide dismutase (EcSOD) according to the manufacturer's instructions (Bioassay, Human Extracellular Superoxide Dismutase [Cu-Zn] ELISA Kit, China).

Statistical Analysis:

The data were analyzed using SPSS statistical software version 23. Descriptive statistics are presented as means ± standard deviations (SD). Student's t-test, ANOVA test, and Pearson correlation analysis were used as appropriate. A significance level of $P \leq 0.05$ was considered statistically significant.

Results

A total of 167 patients with type 2 diabetes participated in this study, with 101 patients in the control group (without nephropathy) and 66 patients in the diabetic nephropathy (DN) group. The DN group was further divided into two subgroups: microalbuminuria (n=59) with an ACR between 30 and 300 mg/g, and macroalbuminuria (n=7) with an ACR above 300 mg/g. The estimated glomerular filtration rate (eGFR) was categorized into four stages: 1, 2, 3a, and 3b.

The EcSOD enzyme concentration did not show a significant difference between the control group and the DN group (P value = 0.420), nor between the microalbuminuria and macroalbuminuria subgroups of DN (P value = 0.787). Similarly, no significant difference was detected in the enzyme concentration when comparing the control group with the DN subgroups. The analysis of enzyme

levels according to eGFR stages also did not reveal significant variations (P value = 0.626). Table 1 presents these results. Furthermore, there was no correlation between the EcSOD concentration and any demographic or biochemical parameters between the two groups. However, when comparing the EcSOD concentration among different BMI categories, a significant difference was observed between normal weight (117.24 ± 68.05) and obese (163.19 ± 56.85) participants in the normoalbuminuria group, with a P value of 0.018. Additionally, the urea concentration showed a positive correlation (r = 0.291) with the EcSOD concentration in the DN group (P value = 0.019).

Table 1: Extracellular Superoxide Dismutase (EcSOD) results among study individuals

Study group	EcSOD ng/dL (±SD)	p-value	
No-nephropathy	157.68 (±66.67)	0.420*	
Diabetic Nephropathy	166.18 (±66.02)		
Microalbuminuria	166.95 (±68.83)	0.787	0.403*
Macroalbuminuria	159.73 (±36.96)		0.936*
eGFR stages			
Stage 1	159.66 (±72.74)	0.626	
Stage 2	168.54 (±57.35)		
Stage 3a	143.08 (±64.57)		
Stage 3b	174.69 (±26.36)		

* P value was calculated in reference to the diabetic patients without nephropathy. eGFR: Estimated Glomerular Filtration Rate.

The baseline characteristics of the participants are presented in Tables 2 and 3.

Table 2: Baseline characteristics of the study groups, according to the presence of nephropathy:

Variable	No-nephropathy	Nephropathy	p-value
Age (years) (±SD)	52.3 (±7.78)	50.7 (±9.66)	0.229
Male gender	33 (32.7%)	32 (48.5%)	
Female gender	68 (67.3%)	34 (51.5%)	
Duration (years) (±SD)	9.0 (±5.7)	9.3 (±5.8)	0.731
Height (cm) (±SD)	161.60 (±9.38)	162.91 (±9.79)	0.389
Weight (Kg) (±SD)	80.47 (±18.78)	81.18 (±18.61)	0.809
BMI (Kg/m2) (±SD)	30.58 (±5.61)	30.68 (±6.96)	0.950
Hypertension (%)	33 (32.7%)	28 (42.4%)	0.209
ACR mg/g (±SD)	13.44 (±8.42)	203.64 (±376.8)	<0.0001
eGFR ml/min 1.73 m2 body surface area (±SD)	99.91 (±38.42)	102.06 (±37.56)	0. 725

BMI: Body Mass Index, ACR: Albumin Creatinine Ratio, eGFR: Estimated Glomerular Filtration Rate, n: number of individuals.

Table 3: Baseline characteristics of the diabetic nephropathy sub-groups:

Variable	No nephropathy	Nephropathy sub-groups			
		Micro-albuminuria	p-value*	Macro-albuminuria	p-value
Age (years) (±SD)	52.3 (±7.78)	50.7 (±9.62)	0.255	50.3 (±10.73)	0.906
Male gender	44 (43.6%)	26 (44.1%)		6 (85.7%)	0.512*
Female gender	57 (56.4%)	33 (55.9%)		1 (14.3%)	
Duration (years)(±SD)	9.0 (±5.7)	9.4 (±5.81)	0.676	9.1 (±5.55)	0.978*
Height (cm) (±SD)	161.60 (±9.38)	162.20 (±9.71)	0.701	161.60 (±9.38)	0.50*

Weight (Kg) (±SD)	80.47 (±18.78)	80.75 (±19.14)	0.928	80.47 (±18.78)	0.546*
BMI (Kg/m2) (±SD)	30.62 (±5.62)	31.01 (±7.07)	0.675	30.58 (±5.60)	0.705*
Hypertension (%)	33 (32.7%)	24 (40.7%)	0.315	4 (57.1%)	0.205*
ACR (mg/g) (± SD)	13.44 (±8.42)	103.47 (±66.43)	<0.001	1048 (±751.83)	<0.001*
eGFR ml/min 1.73 m^2 body surface area (±SD)	99.91 (±38.42)	102.40 (±38.29)	0.697	99.29 (±33.22)	0.967*

* P value was calculated in reference to the diabetic patients without nephropathy. BMI: Body Mass Index, ACR: Albumin Creatinine Ratio, eGFR: Estimated Glomerular Filtration Rate.

Glucose concentration and HbA1c levels were comparable between the groups. Detailed information about the studied parameters is provided in Tables 4 and 5. No significant differences were observed in the chemical parameters between the control group and the DN group. Furthermore, when comparing each DN subgroup with the control group, no significant variations in the enzyme concentration were found.

Table 4: Biomarkers values of study groups

Parameter	No nephropathy	Nephropathy	p-value
RBS g/dL	213.7(±95)	194 (±89)	0.221
HbA1C (%)	9.3(±2.2)	8.8(±2.1)	0.169
Urea mg/dL (±SD)	31(±12)	31(±9.2)	0.722
Creatinine mg/dL (±SD)	0.87(±0.36)	0.90(±0.37)	0.597
TG mg/dl (±SD)	146(±97)	140(±85)	0.703
Total cholesterol mg/dL (±SD)	163(±51)	163(±43)	0.991
HDL mg/dL (±SD)	40(±15)	36(±13)	0.204
LDL mg/dL (±SD)	78(±37)	83(±38)	0.621
vLDL mg/dL (±SD)	29(±19)	27(±17)	0.683

$HbA1_C$: glycosylated hemoglobin A1; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; vLDL: very low density lipoprotein.

Table 5: Biomarkers values of the diabetic nephropathy sub-groups:

Variable	No nephropathy	Nephropathy sub-groups			
		Micro-albuminuria	p-value*	Macro-albuminuria	p-value
Blood Glucose g/dL	213.7 (±95)	198 (±91)	0.337	163 (±76)	0.208*
$HbA1_{C\ (\%)}$	9.3(±2.2)	8.8 (±2.1)	0.215	8.6 (±2.1)	0.393*
Urea mg/dL (±SD)	31(±12)	30 (±9)	0.645	33 (±7.3)	0.791*
Creatinine mg/dL (±SD)	0.87 (±0.36)	0.89 (±0.36)	0.721	0.98 (±0.52)	0.447*
TG mg/dL (±SD)	146(±97)	138 (±89)	0.608	159 (±49)	0.718*
Total cholesterol mg/dL (±SD)	163(±51)	160 (±40)	0.692	181 (±59)	0.387*
HDL mg/dL (±SD)	40(±15)	36 (±14)	0.273	35 (±8)	0.391*
LDL mg/dL (±SD)	78(±37)	77 (±33)	0.909	107 (±53)	0.101*

vLDL mg/dL (±SD)	29(±19)	27 (±17)	0.591	31 (±9)	0.728*

* P value was calculated in reference to the diabetic patients without nephropathy. $HbA1_C$: glycosylated hemoglobin A1; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; vLDL: very low density lipoprotein.

Discussion:

The present study did not find a significant difference in EcSOD concentration between the diabetic-only group and the early DN group. Similarly, the results of urea and creatinine levels did not show significant differences, which may be attributed to nephropathy being an early stage of kidney disease that does not significantly impact overall kidney function.

The variability in research findings regarding the activity of total SOD enzyme in diabetic patients can be attributed to most studies focusing on total SOD activity, without examining the concentration and activity of each isozyme separately [17]. Some studies reported increased SOD activity in diabetic patients [18], while others reported decreased activity [19], or no significant differences [20]. Consequently, the evidence regarding EcSOD's involvement in DN, particularly in the early stages, remains inconclusive.

Notably, studies conducted on Japanese renal failure patients and hemodialysis patients showed higher EcSOD concentrations compared to healthy individuals [21]. Similarly, a Taiwanese study revealed higher EcSOD levels in diabetic patients with overt chronic kidney disease [22]. Furthermore, Galvan and colleagues demonstrated that mitochondria are the primary source of reactive oxygen species (ROS) in mice with DN [23], suggesting that SOD2, located in the mitochondria, may play a role in removing superoxide ions. Interestingly, Fujita and his team found elevated levels of SOD1, located in the cytoplasm, in DN patients [14], suggesting that both SOD1 and SOD2 isozymes may eliminate ROS in the early stages of DN without requiring an increase in EcSOD. These findings align with a previous study on diabetic mice conducted by Fujita et al., which showed that only SOD1 deficiency, not SOD3 (EcSOD) deficiency, resulted in significant proteinuria and oxidative stress. Consequently, they proposed that EcSOD might not play a prominent role in the etiology of DN.

Conversely, other studies have reported a correlation between EcSOD concentration and diabetic nephropathy. Kimura et al. demonstrated reduced serum EC-SOD levels associated with higher proteinuria and greater severity of DN in individuals with type 2 diabetes [24]. Guo's study found that EcSOD deficiency contributes to the development of chronic kidney disease and renal failure in rat kidneys [25]. Additionally, Fujita et al. investigated the expression of renal SOD isoforms using immunofluorescence histochemistry and found that both SOD1 and EcSOD isozymes play a crucial role in the development of overt DN, with SOD3 expression observed in the glomerular capillary and arterial/arteriolar wall [26]. In contrast, Hong's study on diabetic mice showed a significant reduction in renal EcSOD expression [13].

Further research is warranted to elucidate the precise mechanism through which persistent hyperglycemia affects the renal EcSOD antioxidant defense system. These investigations will provide valuable insights into the etiology of DN and contribute to the development of improved treatment approaches for this condition. Additionally, repeating the protein (or albumin) to creatinine ratio at least three times for patients initially diagnosed with nephropathy may help exclude certain cases. Unfortunately, due to the constraints imposed by the COVID-19 pandemic and the associated challenges, this was not feasible in the present study.

Conclusion

According to our results, the concentration of EcSOD has not been shown to be associated with the development of nephropathy in diabetic patients. Furthermore, no significant relationship was found between EcSOD concentration and the severity of diabetic nephropathy, as evidenced by the lack of

variation in EcSOD concentration between microalbuminuria and macroalbuminuria stages, as well as different eGFR stages.

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Conflicts of interest:

The authors have no financial or proprietary interests in any material discussed in this article.

Ethics approval:

Approval was obtained from the ethics committee of University of Kufa. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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