DJS Vol. 42 (2020)- pp.100-107 - ISSN: 1012-5965

Delta Journal of Science
Available online at
https://djs.journals.ekb.eg/

Research Article **BIOCHEMISTRY**

Erythrocyte GST activity in type 2 diabetes with and without nephropathy

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KEY WORDS

Diabetic nephropathy; Oxidative stress; Glutathione S-transferase

ABSTRACT

Diabetic nephropathy (DN) is the main cause of chronic kidney disease, and represents the most common and serious complication of diabetes. The occurrence and progression of DN are closely related to oxidative stress. Excessive reactive oxygen species (ROS) induced by hyperglycemia are involved in direct oxidation and damage of deoxyribonucleic acid (DNA), proteins, and lipids. Glutathione S-transferases have central roles in the cellular detoxification of a diverse group of exogenous and endogenous harmful compounds. The present study aims to clarify the possible role of erythrocyte glutathione S-transferase activity in type 2 diabetic patients with and without nephropathy. This study included 60 diabetic patients (20 diabetics with normoalbuminuria, 20 diabetics with microalbuminuria, 20 diabetics with macroalbuminuria) and 20 healthy volunteers as a control group. Glutathione S- transferase (GST), superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) activities, and Reduced glutathione (GSH) level were significantly lower in diabetic patients with and without nephropathy as compared to control. Malondialdehyde (MDA) level was significantly higher in diabetic patients with and without nephropathy as compared to control. GST, SOD, GPx, CAT, GSH and MDA were positively correlated with estimated glomerular filtration rate and negatively correlated with albumin creatinine ratio. It was concluded that erythrocyte GST may be used as a biomarker to differentiate between different groups of nephropathy.

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. Diabetes is a major health problem worldwide. In 2014, according to World Health Organization (WHO), at least 422 million people suffered from type 2 diabetes. Its incidence is increasing rapidly, and it is expected that by 2040, this number will rise to 642 million [2]. In Egypt, type 2 diabetic cases among adults aged 40 – 59 years were 7.8 million in 2015, and it is expected that this number will jump up to 13.1 million by 2035 [3]. Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD). The classical definition of DN is a progressive rise in urinary albumin excretion (UAE), coupled with increased blood pressure, leading to a decline of glomerular filtration rate (GFR), and eventually end-stage renal failure. About 35–50 % of patients with type 1 or type 2diabetes develop evidence of nephropathy. DN form about 40% of new cases of ESRD [4]. Glutathione S-transferase (GST) is a family of enzymes that detoxify reactive electrophiles, products of oxidative stress, and suspected carcinogenic compounds through conjugation with reduced glutathione (GSH) [5]. GST is considered a family of phase II detoxification enzymes, acts as an antioxidant through inactivation of endogenous unsaturated aldehydes, quinines, epoxides, and hydroperoxides formed as secondary metabolites during the oxidative stress, thus playing a key role in protecting cell types of various origin, including vascular smooth muscle cells and endothelial cells against oxidant damage. The aim of our study was the evaluation of erythrocyte GST, and another antioxidant enzyme (glutathione peroxidase (Gpx), superoxide dismutase (SOD), and GSH in different cases and severity of diabetic nephropathy. The severity of diabetic nephropathy was determined according to the leakage of albumin from the nephron.

Material and methods

Human subjects

This study was approved by the local Ethical Committee from Tanta University. Approval code: 31314/01/17; all participants gave the written informed consent of their participation. The study included 60 patients with type 2 diabetes and 20 healthy control subjects (group l). Patients with diabetes were divided into 20 patients with normoalbuminuria (group ll), 20 patients with microalbuminuria (group lll), and 20 patients with macroalbuminuria (group lV). Patients

were selected from those admitted to Internal Medicine Department, Tanta University Hospital, their ages ranged from 50 - 62 years. At the time of blood collection, information was recorded for all subjects, including height and weight. All volunteers were asked to answer a questioner about family history of diabetic diseases. Diabetic patients with uncontrolled hypertension, end -stage renal disease, under dialysis, liver disease, cardiac disease, and urinary tract infection were excluded from the study.

Methodology

A full history was taken with particular emphasis on the duration of diabetes, urinary symptoms, and symptoms of microvascular complications of diabetes, history of any other associated disease, hypertension, cigarette smoking, hypercholesterolemia and therapeutic history. 10 ml of venous blood samples were collected from each subject and divided into: 1 ml of blood was collected in sodium fluoride test tube for determination of fasting blood glucose level (glucose was measured by Spinreact, 2 ml of blood were collected in EDTA sterile vacutainer for determination of glycosylated hemoglobin percentage using Nycocard reader kit (1042184). 2 ml of blood were collected in dry centrifuge tubes then centrifuged for 5 minutes at 3000 rpm, the serum was used for determination of creatinine (11502) and urea levels (21516) Kidney function tests were measured by Biosystem kits). 5 ml of whole blood were collected in EDTA vacutainer tube for determination of Glutathione S-transferase (GT 2519) activity, Glutathione peroxidase activity (GP 2524) , superoxide dismutase activity (SD 2521) (using kits from Biodiagnostic), catalase activity according to the method of [6], Reduced Glutathione level was measured by the method of [7] and MDA level by the thiobarbituric acid method [8].

Statistical analysis

Statistical analysis of the data was performed by Graph Pad Prism version 6.00 for (Graph Pad Software Inc., San Diego, California USA). Descriptive data were given as mean ±SD. Differences among groups were tested using t-test. One- way ANOVA test was applied to analyse the significance of difference among all groups and control. Chi-squared test was applied to test the association between distribution of sex and the studied groups. Statistical significance was defined as the probability of P value < 0.05.

Results

Table (1) shows distribution of age, body mass index and diabetic duration in patient

groups and control. There is a significant difference between the studied groups, age, and diabetic duration but there is no significant difference in BMI in the studied groups.

Table (2) shows Sex distribution in patient groups and control, there is no significant difference in the studied groups p>0.05 and chi square X2 = 5.3. Table (3) shows kidney function tests in the studied groups. Urea, creatinine and albumin creatinine ratio were significantly increased in diabetics with and without nephropathy as compared to control. While, eGFR was significantly decreased in diabetics with and without nephropathy as compared to control. Table (4) shows antioxidant activities in the studied groups. Erythrocyte GST, SOD, GPx, CAT were significantly decreased in diabetic patients with and without nephropathy as compared to control. Table (5) shows erythrocyte GSH and plasma MDA levels. GSH level was significantly decreased in diabetics with and without nephropathy as compared. MDA level was significantly increased in diabetic patients with and without nephropathy as compared to control.

Table 1: Age, BMI and diabetes duration in the studied groups

Parameters	Control group (n= 20) (I)	Type 2 diabetic patients (n= 60)		
		DM with normoalbumin-uria (n= 20) (II)	DM with microalbumi n-uria (n= 20) (III)	DM with macroalbumi n-uria (n= 20) (IV)
Age (years) Range Mean ±S.D	50 – 60 55.4 ± 3.0	52 - 60 56.1 ± 2.6	53 - 61 56.9 ± 2.5	53 - 62 57.5 ± 2.9
F test *P* value	2.04 0.1147			
BMI (kg/m^2) Range Mean ±S.D	22.0 –26.0 24.2 ± 1.5	27.3 – 30.2 28.7 ± 1.0	28.0 – 32.0 29.3 ± 1.3	28.5 – 32.4 30.2 ± 1.2
F test *P* value	93.15 < 0.0001*			
Scheffe test	0.0001 I vs II, *P* = 0.0001 I vs III, *P*= 0.0001 I vs IV, *P* = II vs III, p=0.05 II vs IV, p= 0.01 III vs IV, p= NS			
DM duration (years) Range Mean ±S.D		6 - 11 8.5 ± 1.8	7- 13 9.9± 1.7	7 - 15 11.0 ± 2.4
F test *P* value	7.5 0.0012*			
Scheffe test	II vs III, *P* = NS II vs IV, P = 0.001 III vs IV, p = NS			

*Significant (*P*<0.05); NS= Non significant.

Table 2: Sex distribution in patient groups and control

Sex	Control group (n= 20) (I)		Type 2 diabetic patients (n= 60)					
			DM with normoalbumi n-uria (n= 20) (II)		DM with microalbumi n-uria (n= 20) (III)		DM with macroalbu min-uria (n= 20) (IV)	
	n	%	n	%	n	%	n	%
Male	11	55	13	65	14	70	8	40
Female	9	45	7	35	6	30	12	60
X^2 *P* value	5.333 0.1490 NS							

NS= Non significant; X^2, chi-squared distribution

Table 3: Kidney function tests in the studied groups

Parameters	Control group (n= 20) (I)	Diabetic patients (n= 60)		
		DM with normoalbumin-uria (n= 20) (II)	DM with microalbumin-uria (n= 20) (III)	DM with macroalbumin-uria (n= 20) (IV)
Creatinine (mg/dl) Range Mean ±S.D	0.7 - 1.0 0.82 ± 0.1	0.7 - 1.6 1.02 ± 0.2	1.3 – 2.5 1.53 ± 0.4	1.4 - 3.0 1.94 ± 0.3
F test *P* value	66.1 0.0001*			
Scheffe test	0.0001 0.0001, I vs IV, *P* = NS, I vs III, *P* = I vs II, *P* = 0.0001 III vs IV, *P* = 0.0001 0.0001, II vs IV, *P* = II vs III, *P* =			
Urea (mg/dl) Range Mean ±S.D	24 - 33 28.4 ± 2.5	30 - 50 38.4 ± 6.9	43 - 75 57.2 ± 10.8	59 - 100 74.3 ± 12.9
F test *P* value	97.5 0.0001*			
Scheffe test	0.0001 0.0001, I vs IV, *P* = 0.01, I vs III, *P* = I vs II, *P* = 0.0001 0.0001 III vs IV, *P* = 0.0001, II vs IV, *P* = II vs III, *P* =			
eGFR (mL/min per 1.73 m2) Range Mean ±S.D	53 – 129 101.4 ± 19.9	50 – 87 71.8 ± 10.5	36 - 60 52.7 ± 6.8	32 - 37 33.6 ± 1.9
F test *P* value	119.7 0.0001*			
Scheffe test	0.0001 0.0001, I vs IV, *P* = 0.0001, I vs III, *P* = I vs II, *P* = 0.0001 0.0001, II vs IV, *P* = II vs III, *P* = 0.0001 III vs IV, *P* =			
ACR (mg/gCr) Range Mean ±S.D	6 - 14 7.9 ± 1.9	9.5 – 28 17.1 ± 6.3	40 - 190 87.2 ± 35.6	430 - 763 581.3 ± 108.1
F test *P* value	462.3 0.0001*			
Scheffe test	0.0001 0.001, I vs IV, *P* = NS, I vs III, *P* = I vs II, *P* = 0.0001III vs IV, *P* = 0.0001 0.001, II vs IV, *P* = II vs III, *P* =			

*Significant (P<0.05); eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio

Table 4: Erythrocyte glutathione S-transferase, superoxide dismutase, and glutathione peroxidase and catalase activities in the studied groups

Parameters	Control group (n= 20) (I)	Diabetic patients (n= 60)		
		DM with normoalbumin-uria (n= 20) (II)	DM with microalbumin-uria (n= 20) (III)	DM with macroalbumin-uria (n= 20) (IV)
GST(U/g Hb) Range Mean ±S.D	52 – 64 58.8 ± 3.7	39 – 47.5 43.2 ± 2.7	35 – 40 37.7 ± 1.6	22.2 – 25.2 23.7 ± 0.97
F test *P* value	670.3 0.0001*			
Scheffe test	0.0001* 0.0001*, I vs IV, *P* = 0.0001*, I vs III, *P* = I vs II, *P* = 0.0001* 0.0001* III vs IV, *P* = 0.0001*, II vs IV, *P* = II vs III, *P* =			
SOD(U/g Hb) Range Mean ±S.D	17.2–25.5 20.2 ± 2.8	13 – 15.5 14.1 ± 0.82	11.5 – 13.2 12.3 ± 0.55	11 – 12.8 11.9 ± 0.54
F test *P* value	124.8 0.0001*			
Scheffe test	0.0001*, I vs IV, *P* =0.0001* 0.0001*, I vs III, *P* = I vs II, *P* = NS 0.0001* III vs IV, *P* = 0.01*, II vs IV, *P* = II vs III, *P* =			
GPx(mU/mL) Range Mean ±S.D	442 – 452 447.9 ± 3.1	413 – 419 416.5 ± 2.0	397 - 405 401.2 ± 2.4	378 - 387 382.6 ± 2.7
F test *P* value	2188 0.0001*			
Scheffe test	0.0001* 0.0001*, I vs IV, *P* = 0.0001*, I vs III, *P* = I vs II, *P* = 0.0001* III vs IV, *P* = II vs III, *P* = 0.0001*, II vs IV, *P* = 0.0001*			
CAT(µmol /min/g Hb) Range Mean ±S.D	65 – 82 73.4 ± 5.2	47 – 66 56.5 ± 5.9	36 – 58 45.6 ± 6.2	25 – 39 30.8 ± 4.4
F test *P* value	214.7 0.0001*			
Scheffe test	0.0001* 0.0001*, I vs IV, *P* = 0.0001*, I vs III, *P* = I vs II, *P* = 0.0001* 0.0001* III vs IV, *P* = 0.0001*, II vs IV, *P* = II vs III, *P* =			

*Significant (P<0.05); GST, glustathione S-transferase; SOD, superoxide dismutase; GPx, glutathione peroxidase; CAT, catalase

Table 5: Erythrocyte reduced glutathione and plasma malondialdehyde levels in the studied groups

Parameters	Control group (n= 20) (I)	Diabetic patients (n= 60)		
		DM with normoalbumin-uria (n= 20) (II)	DM with microalbumin-uria (n= 20) (III)	DM with macroalbumin-uria (n= 20) (IV)
GSH (µmol/g Hb) Range Mean ±S.D	52 – 69 58 ± 5.3	46 – 53 49.6 ± 2.1	42 – 50 45.9 ± 2.6	37 – 47 41.8± 3.0
F test *P* value	77.6 0.0001*			
Scheffe test	0.0001* 0.0001*, I vs IV, *P* = 0.0001* I vs III, *P* = I vs II, *P* = 0.0001* III vs IV, *P* =0.01* 0.01*, II vs IV, *P* = II vs III, *P* =			
MDA (nmol/ mL) Range Mean ±S.D	4 – 4.7 4.4 ± 0.2	6.1 – 6.9 6.6 ± 0.2	7 – 7.7 7.3 ± 0.2	7.3 – 7.9 7.6 ± 0.1
F test *P* value	1007 0.0001*			
Scheffe test	0.0001* 0.0001I vs III, *P* 0.0001* =, I vs IV, *P* = I vs II, *P* = NS 0.0001* III vs IV, *P* = II vs III, *P* = 0.0001*, II vs IV, *P* =			

*Significant (P<0.05); GSH, reduced glutathione;

MDA, malondialdehyde; NS: Non significant

Discussion

Diabetic nephropathy (DN) is the main cause of chronic kidney disease, and represents the most common and serious complication of diabetes. The exact pathogenesis of DN is complex and not elucidated. Several factors and mechanisms contribute to the development and outcome of DN. An early diagnosis and intervention may slow down disease progression [5]. The occurrence and progression of DN are closely related to oxidative stress. Excessive ROS, which is induced by hyperglycemia, is involved in oxidative stress causing direct oxidation and damage of deoxyribonucleic acid (DNA), proteins and lipids [9]. Hyperglycemia is associated with the production of ROS in diabetic patients .The production of ROS is considered to be one of the major causes of diabetic complications, including nephropathy[10].

Glutathione S transferases (GSTs) represent a superfamily of enzymes involved in cell protection and detoxification. The main function of these enzymes is the conjugation of GSH to toxic hydrophobic compounds provided by an electrophilic center. This reaction facilitates toxins inactivation and renal elimination of a large number of toxins [11]. GSTs constitute one of the major components of phase II drug-metabolizing enzyme and antioxidant systems .Therefore, there is an increasing interest in the role that polymorphisims in phase I and phase II detoxification enzymes may play role in the etiology and progression of diseases. [12,13]. In the current study, the activity of glutathione S- transferase was significantly decreased in diabetic groups with and without nephropathy as compared to control (Table 4). These findings are supported by [14,15,16] who reported that GST activity was decreased in diabetic patients as compared to control. Conversely, [17] reported that GST activity was significantly increased in diabetic patients as compared to controls, then reached its

highest values in diabetics with nephropathy. In the present study, the activity of superoxide dismutase (SOD) was significantly decreased in diabetic groups with and without nephropathy as compared to control (Table 4). Similar results were obtained by [18,19] who reported that SOD activity was significantly decreased in diabetics with and without nephropathy as compared to control due to higher oxidative stress produced by high glucose levels. In the current study, the activity of glutathione peroxidase (GPx) was significantly decreased in diabetic groups with and without nephropathy as compared to control. Similar results were obtained by [18,20] and [21] who reported that GPx activity was significantly decreased in diabetics with and without nephropathy as compared to control. In our study, catalase activity was significantly decreased in diabetic groups with and without nephropathy as compared to control. These findings are supported by [22,23]. A further reduction in catalase activity in patients with diabetic nephropathy may be due to a higher magnitude of oxidative stress in these subjects. On the contrary, [24] reported that catalase activity was significantly increased in diabetics with and without nephropathy as compared to control. Moreover, [25] reported an increase in CAT activity, which overcomes the damaging effect of the erythrocyte membrane from oxidative attack. In our study, reduced glutathione(GSH) level was significantly decreased in diabetics with and without nephropathy as compared to control. This coincides with [18] reported a significant decrease in GSH level in diabetics as compared to controls. Glutathione is thiol-containing tripeptides which in its reduced form (GSH) is present in living cells at high concentrations. When it reacts with ROS, it gets oxidized to glutathione radical which is regenerated to its reduced form through glutathione reductase activity. A significant decrease in GSH concentration in diabetic groups may be due to conversion of reduced form to oxidized form (GSSH) by excessive production of reactive oxygen species[18]. In the current study, malondialdehyde (MDA) level was significantly increased in diabetic groups with and without nephropathy as compared to control. Similar to our results, [20] presented an increased MDA level in diabetics with and without nephropathy because of reduced activity of most of the antioxidant enzymes.

Conclusion

Oxidative stress (OS) and antioxidant status may be linked with glycemic control and probably contribute to the development of diabetic complications. It also suggested that an increase in GST could be an adaptive and protective response in patients with diabetes from the progression of DN. MDA and GSH

levels preceding the development of diabetes complications might be considered good indicators for evaluating OS in complications of T2DM such as DN. Thus, the monitoring of the studied oxidative stress parameters as early predictors of DN in patients of T2DM should be considered. Antioxidants could be useful in the management of DN to prevent progressive deterioration and target organ damage however; further studies involving long-term clinical trials may help to assess the efficacy of these therapeutic agents.

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تقييم نشاط الجلوتاثيون إس ترنسفيراز فى اغشية كرات الدم الحمراء في مرضي البول السكري من النوع الثاني المصحوب وغير المصحوب بالإعتلال الكلوي

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يعتبر مرض الاعتلال الكلوي السكري مشكلة صحية كبرى فى مصر والعالم وهو مرض معقد تتدخل فيه العوامل البيئية والوراثية المختلفة. ولقد وجد أن الإجهاد التأكسدى يسبب الإعتلال الكلوي . ومن المعروف أن إنزيم الجلوتاثيون إس ترانسفيراز يلعب دورا أساسيا فى إزالة سمية مولدات الأكسدة. يهدف هذا البحث إلى دراسة العلاقة بين التعدد الشكلى لجين الجلوتاثيون إس ترانسفيراز إم ١ وتى ١ ودلائل الإجهاد التأكسدى فى المرضى المصريين المصابين بالإعتلال الكلوي السكري. وقد أجريت هذه الدراسة على ٦٠ مريضا مصابين بالإعتلال الكلوي السكري بالإضافة إلى ٢٠ شخصا من الأصحاء كمجموعة ضابطة . وقد تم إجراء فحص إكلينيكى كامل وعمل فحوصات معملية شملت: نسبة السكر في الدم – وظائف الكلي- نسبة الهيموجلوبين السكري في الدم- مستوى المالون ثنائى الألدهيد فى البلازما – مستوى الجلوتاثيون المختزل وأنشطة إنزيمات كتاليز ، سوبرأوكسيد ديسميوتيز ، جلوتاثيون بيروكسيديز ، جلوتاثيون إس ترانسفيراز فى كرات الدم الحمراء . وقد أوضحت هذه الدراسه إرتفاع المالون ثنائى الألدهيد فى البلازما فى مرضى البول السكري بالمقارنة بالمجموعة الضابطة. وكذلك وجد إنخفاض ذو دلالة إحصائية فى مستوى الجلوتاثيون المختزل وأنشطة إنزيمات كتاليز ، سوبرأوكسيد ديسميوتيز ، جلوتاثيون بيروكسيديز ، جلوتاثيون إس ترانسفيراز فى كرات الدم الحمراء فى مرضى البول السكري بالمقارنة بالمجموعة الضابطة. نستنتج من هذه الدراسه الإرتباط الواضح بين الإجهاد التأكسدي ونسبة السكر في الدم ودوره في حدوث مرض الإعتلال الكلوي السكري.
يوصى هذا البحث بمزيد من الدراسات الإكلينيكية المستقبلية فى إستعمال مضادات الأكسدة كمحاولة لمنع حدوث وعلاج مرض الإعتلال الكلوي السكري ومضاعفاته على أعضاء الجسم المختلفة.