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EFFECTS OF TRIMETAZIDINE ON OXIDATIVE STRESS IN STREPTOZOTOCIN-INDUCED DIABETIC NEPHROPATHY IN RATS

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ABSTRACT

Oxidative stress induced by hyperglycemia in diabetes mellitus is a major cause for development and progression of diabetic microvascular complications such as nephropathy. Thus, the protective action of trimetazidine "TMZ" against oxidative stress was investigated in a rat model of diabetic nephropathy. Diabetes was induced in male Sprague -Dawley rats using streptozotocin (65 mg/kg). Either TMZ (10 mg/kg) or captopril (50 mg/kg) was gavaged daily for 12 weeks. After the end of the experimental period, renal functions and renal oxidative stress markers were assessed. Either captopril or TMZ exhibited significant improvement of the renal function that was correlated with significant decrease in the renal

oxidative stress markers. In conclusion, the antioxidant property of TMZ may offer a potential therapeutic source for the treatment of diabetic nephropathy.

Keywords : diabetic nephropathy, oxidative stress, renal functions, trimetazidine.

INTRODUCTION

Diabetic nephropathy associated with diabetes mellitus is a leading common cause of end stage renal disease (ESRD) in many countries (1). Renal disease is usually attributed to metabolic consequences of abnormal glucose regulation manifested by elevated blood and tissue levels of glycosylated proteins and hemodynamic changes within the kidney tissue (2).

Diabetic nephropathy is characterized by a progressive accumulation of extracellular matrix components in the glomerular mesangium and tubular interstitium, which eventually leads to proteinuria and renal failure (3). The exact mechanisms underlying the evolution of diabetic nephropathy are complex and not well defined. The microvascular complications of diabetes share a common pathophysiology that may be explained as a direct or indirect consequence of hyperglycemia-mediated overproduction of reactive oxygen species (ROS) that occurs before structural changes and mesangial matrix deposition (4). ROS attacks the unsaturated fatty acid in the biomembrane to yield lipid peroxidation such as ketone, hydroxyl radical and malondialdehyde (MDA) known confounders of nephropathy in type 2 diabetes (5). ROS-mediated transcription factors nuclear factor kappa beta (NF- κ B) and activated protein-1 (AP-1) which lead to activation of human transforming growth factor beta-1 (TGF- β 1) and deposition of extracellular matrix and tissue fibrosis (6).

So, this microvascular deterioration could be prevented either by

modulating the blood glucose levels or by the inhibition of free radicals accumulation (7), and among several microvascular disorders, nephropathy can be improved by the use of antioxidants (8,9).

Trimetazidine "TMZ" is a piperazine derivative (1-(2,3,4-trimethoxybenzyl)-piperazine dihydrochloride) with anti-ischemic properties as TMZ decreases ischemic stress and improves cardiac performance during ischemia (10). At the cellular level, TMZ preserves ATP production and reduces intracellular acidosis and calcium overload and thereby maintains the cellular homeostasis (10). It has been also improved that TMZ has antioxidant properties *in vitro* (11, 12) and *in vivo* (13,14). TMZ decreases oxidative damage to mitochondria and protects tissues from ischemia reperfusion-induced damage to mitochondrial respiration (11).

Thus based on reported properties of TMZ, we investigated the antioxidant and the protective effect of TMZ against the development and the progression of diabetic nephropathy in comparison to captopril in rats.

METHODS

Drugs : Trimetazidine dihydrochloride (metacardia tablets 20 mg, Global Napi Pharmaceuticals, Egypt) and captopril (Capoten, tablets 25mg Bristol-Myers Squibb, Egypt).

Study design : This study was carried on male Sprague-Dawley rats weighing 300 to 350 gm. They were maintained under standard conditions of temperature $22 \pm 2^\circ\text{C}$ with regular 12h light/12 h dark cycle and allowed free access to standard laboratory food and water. All experimental procedures were performed in accordance with guidelines of the Institutional Animal Care and Use Committee of Faculty of Medicine, Mansoura University. The rats were divided into two groups; Control and Streptozotocin (STZ)-induced diabetic nephropathy rats. Each group was subdivided into three groups (8 animals in each group); non-treated group: rats received saline (1ml); captopril group: rats treated with captopril (50 mg/kg body weight) (15) and TMZ group: rats treated with TMZ (10 mg/kg body weight /day) (16).

Diabetes was induced in the second group by intraperitoneal injection of STZ 65 mg/kg body weight (Sigma Chemical Co., St Louis, MO) dissolved in 0.1mmol/l sodium citrate buffer, pH 4.5.(5) Seventy two hours after STZ injection diabetes mellitus was confirmed by measuring venous blood glucose levels. Rats with fasting blood glucose level less than 300 mg/dl were excluded from the experiment. The final number of animals of each subgroup was eight. The rats received saline or medication by oral gavage via gastric tube once daily for twelve weeks .

At the end of the experimental period, twenty four-hour urine samples were collected in individual metabolic cages for measurement of urinary albumin excretion (UAE) one day prior to sacrifice. Urine microalbumin concentration was measured according to the rapid colorimetric method using commercial kit (Randox Laboratories Ltd., Antrim, United Kingdom) (17).

On the next day, rats were weighed and sacrificed after fasting for 12 h and blood and kidney samples were collected. Blood were col-

lected and centrifuged at 2000g for 10 min to measure serum glucose and creatinine. The fasting serum glucose was measured according to the glucose oxidase method (18). The serum creatinine was determined using creatinine-colorimetric kit (Diamond diagnostic, USA) (19). Kidneys were removed, weighed and kidney / body weight ratio (KW/BW%) was calculated. The kidneys were homogenized (1 g/10 ml ice-cold potassium chloride, 150 mM). The homogenate was then stored at -80°C till time of assay of the oxidative stress markers. The lipid peroxidation product; MDA was determined on the base of its reaction with thiobarbituric acid (TBA) to form a pink complex with absorption maximum at 535 nm using the method described by Uchiyama and Mihara (20). The reduced glutathione (GSH) content in the kidney homogenate was determined using the method described by Van Dooran et al. (21). The basis is the reaction of Ellman's reagent 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) with thiol group of GSH at pH 8.0 to give yellow color of 5-thiol-2-nitrobenzoate anion. The activity of superoxide dismutase (SOD) enzyme in kidney homogenate

was determined according to the method described by Sun and Zigmán (22). This method is based on the ability of SOD to inhibit the auto-oxidation of epinephrine at alkaline pH to adrenochrome and other derivatives, which are easily monitored in the near-UV region of the absorption spectrum. The catalase (CAT) activity was determined by measuring the exponential disappearance of H₂O₂ at 240 nm and expressed as units/mg of protein as described by Aebi (23). The total proteins content in kidney was determined according to the Lowry's method and as modified by Peterson (24).

STATISTICAL ANALYSIS

The statistical analysis was carried out using SPSS version 10 statistical programs (SPSS Inc., Chicago, IL, USA). Differences among groups within an experiment were analyzed by the one-way ANOVA analysis of data followed by post hoc test of Tukey HSD. The results are presented as mean \pm SEM. A P value of <0.05 value was considered significant. Correlation was expressed by Kendall's rank correlation, while regression formulation was obtained by regression

analysis. A P value < 0.05 was considered significant.

RESULTS

The body weight of all diabetic groups was significantly decreased compared with the control groups. Although captopril or TMZ caused increase in the body weight, it is statistically still below the normal weight of the control groups. Meanwhile kidney weight (KW) was significantly increased in the non-treated diabetic group compared with the control group. Treatment of diabetic nephropathy group with either captopril or TMZ caused significant decrease in the KW in comparison to the control groups (table 1).

UAE was significantly increased in diabetic nephropathy group in comparison to the control groups. Either captopril or TMZ - treated diabetic nephropathy group showed significant decrease in UAE versus that of non-treated diabetic group (table 1).

The fasting blood glucose level of the diabetic groups was significantly increased in comparison to the control group, without significant changes

of glucose level between untreated and captopril or TMZ-treated diabetic groups (table 2).

The serum creatinine level was significantly increased in diabetic nephropathy group in comparison to the control groups. Treatment of diabetic nephropathy group with captopril or TMZ caused significant decrease in the serum creatinine as compared to that of non-treated diabetic group (table 2).

Renal MDA in diabetic nephropathy groups was significantly increased while renal SOD, CAT and GSH were significantly decreased as compared to the control groups. Captopril or TMZ treated diabetic nephropathy groups showed significant decrease in renal MDA associated with significant increase in renal SOD and GSH as compared to those of non-treated diabetic group. TMZ only caused significant increase in renal CAT versus those of non-treated diabetic nephropathy group (table 3).

Importantly, there was non-significant difference of the renal

function parameters between captopril and TMZ treated diabetic nephropathy groups. However, the antioxidant effects of TMZ were statistically more significant versus than those of captopril-treated diabetic group.

Correlation and Regression analysis : Kendall's rank correlation analysis and regression analysis of the parameters in table (4) show that either UAE or KW was negatively associated with SOD/ CAT/ GSH, and positively with MDA, respectively

Table (1) : Effect of oral TMZ (10mg/Kg) versus captopril (50mg/Kg) for 12 weeks on the BW, KW, KW/BW% and 24 h UAE in STZ-diabetic nephropathy rats (Mean \pm SEM, n = 8.)

Groups		BW (gm)	KW (gm)	KW/BW%	UAE (mg/24h)
Control group	Non-treated	322 \pm 28.6	2.4 \pm 0.17	0.75% \pm 0.05	0.24 \pm 0.01
	Captopril-treated	316 \pm 25.4	2.1 \pm 0.08	0.66% \pm 0.03	0.21 \pm 0.01
	TMZ-treated	319 \pm 30.1	2.2 \pm 0.14	0.69% \pm 0.05	0.22 \pm 0.02
STZ-diabetic nephropathy group	Non-treated	197 \pm 15.4*	3.8 \pm 0.21*	1.9% \pm 0.14*	2.62 \pm 0.09 *
	Captopril-treated	202 \pm 18.4*	2.2 \pm 0.09 #	1.1% \pm 0.04* #	0.27 \pm 0.02 #
	TMZ-treated	205 \pm 13.5*	2.5 \pm 0.18 #	1.2 \pm 0.01* #	0.28 \pm 0.01 #

Values were considered significantly different in the case of $P < 0.05$

* versus control group

versus non-treated STZ-diabetic nephropathy group

Trimetazidine; TMZ, body weight; BW, kidney weight; KW, urinary albumin excretion; UAE, streptozotocin; STZ

Table (2): Effect of oral TMZ (10mg/Kg) versus captopril (50mg/Kg) for 12 weeks on fasting blood glucose and S.Cr in STZ-diabetic nephropathy rats (Mean \pm SEM, n = 8.)

Groups		Fasting blood glucose (mg/dl)	S.Cr (mg/dl)
Control group	Non-treated	126.2 \pm 11.2	0.84 \pm 0.07
	Captopril-treated	123.6 \pm 10.9	0.85 \pm 0.05
	TMZ-treated	128.4 \pm 12.5	0.91 \pm 0.08
STZ-diabetic nephropathy group	Non-treated	436.0 \pm 26.9*	2.16 \pm 0.09*
	Captopril-treated	442.6 \pm 39.8*	0.91 \pm 0.08 #
	TMZ-treated	427.2 \pm 32.7*	0.93 \pm 0.07 #

Values were considered significantly different in the case of $P < 0.05$

* versus control group

versus non-treated STZ-diabetic nephropathy group Trimetazidine; TMZ, serum creatinine; S.cr, streptozotocin; STZ

Table (3): Effect of oral TMZ (10mg/Kg) versus captopril (50mg/Kg) for 12 weeks on renal MDA, CAT, SOD and GSH in STZ-diabetic nephropathy rats (Mean \pm SEM, n = 8.)

Groups		MDA (nmol/mg protein)	CAT (unit/ mg protein)	SOD (unit/ mg protein)	GSH (nmol/mg protein)
Control group	Non-treated	0.72 \pm 0.04	35.58 \pm 2.61	3.69 \pm 0.29	35.32 \pm 2.86
	Captopril- treated	0.75 \pm 0.06	33.89 \pm 2.82	4.22 \pm 0.32	38.56 \pm 3.11
	TMZ- treated	0.80 \pm 0.08	35.12 \pm 3.11	3.99 \pm 0.27	36.45 \pm 2.98
STZ- Diabetic nephropathy group	Non-treated	2.64 \pm 0.07*	20.5 \pm 1.78*	1.51 \pm 0.12*	16.04 \pm 1.43*
	Captopril- treated	1.95 \pm 0.09* [#]	21.75 \pm 2.47*	2.87 \pm 0.09* [#]	25.65 \pm 1.90* [#]
	TMZ- treated	0.99 \pm 0.08 ^{#5}	30.46 \pm 2.65 ^{#5}	3.44 \pm 0.16 ^{#5}	31.89 \pm 2.57 ^{#5}

Values were considered significantly different in the case of $P < 0.05$

* versus control group

versus non-treated STZ-diabetic nephropathy group

⁵ versus captopril-treated STZ-diabetic nephropathy group

Trimetazidine; TMZ, Malondialdehyde; MDA, reduced glutathione; GSH, Superoxide dismutase; SOD, catalase; CAT, streptozotocin; STZ

Table 4: Correlation and regression analysis among UAE (mg/24hr), KW (gm) and CAT (U/mg protein), SOD (U/mg protein), GSH (nmol/mg protein), MDA (nmol/mg protein).

Y	X	r	p
UAE	CAT	-0.645	<0.001
UAE	SOD	-0.537	<0.001
UAE	GSH	-0.568	<0.001
UAE	MDA	0.675	<0.001
KW	CAT	-0.613	<0.001
KW	SOD	-0.448	<0.05
KW	GSH	-0.425	<0.05
KW	MDA	0.645	<0.001

UAE; urinary albumin excretion, KW ; kidney weight, MDA; Malondialdehyde,

GSH; reduced glutathione, SOD; Superoxide dismutase, CAT; catalase.

DISCUSSION

Our results, STZ-diabetic rats showed signs of renal nephropathy such as increase in kidney weight that were associated with an increase in the serum creatinine and albuminuria. The involvement of oxidative stress in diabetic nephropathy was also demonstrated by the increase of lipid peroxidation products MDA and decrease activities of the enzymatic antioxidants of SOD, CAT and GSH in the renal tissue which correlated with the UAE.

The noticed microalbuminuria in our results are consistent with those of previous reports (25, 26). Much of great interest about microalbuminuria derives from the fact that albumin excretion predicts the onset of overt renal disease in diabetic patients and reflects glomerular dysfunction (27). Several factors have been shown to influence the progression of diabetic nephropathy after onset of albuminuria as TGF- 1, angiotensin II, and advanced glycation end products. These factors are thought to converge and to promote glomerular and tubular fibrogenesis (28).

Correlation analysis indicates that the UAE or K. W. was negatively associated with SOD/ CAT/ GSH, and positively with MDA, respectively which implies that increased lipid peroxidation and decreased antioxidant enzymes in renal tissue may play a role in the progression of diabetic nephropathy (5).

These results are in agreement with others (29) who found that elevated glucose level per se, could cause oxidative stress in isolated rat glomeruli in vitro. Generation of ROS by diabetic hyperglycemia is evident through many biochemical pathways such as glucose autoxidation and protein glycation (30, 31). The diabetic rats had also shown decreased antioxidant activities in the renal tissue that are consistent with those of previous studies (32-34). It is well known that a number of enzymatic systems exist to protect cells from the damage that would be caused by excessive production of ROS(35). Hyperglycemia not only generates ROS but also attenuates antioxidative mechanisms through glycation of the scavenging enzymes (36). It has been suggested that the production of intracellular an-

tioxidant enzymes in response to high glucose may be defective in patients with type 1 diabetes and nephropathy (37). This defect may be part of the genetic predisposition to nephropathy, although there have been no substantive studies of polymorphisms of the genes coding for the antioxidant enzymes (38). Moreover, the decrease in GSH levels during diabetic nephropathy was probably due to its consumption during oxidative stress. Also, increased aldose reductase of the activated polyol pathway in diabetes decreases the GSH level to promote oxidative stress (39).

In our research, captopril normalized the elevated serum creatinine and prevented renal enlargement and albuminuria that occurred in STZ-diabetic nephropathy rats. The renoprotective effect of angiotensin converting enzyme inhibitor was previously established experimentally and clinically (40-42). The renal antioxidant effect of captopril was also shown in our result but with no effect on the renal CAT enzyme activity. These results are in agreement with Gurer et al. (43) who observed that captopril showed decreased MDA concentra-

tions and high GSH level in the kidneys without significant effect on the catalase activity.

In the present study, TMZ improved the renal function as well as ameliorated the oxidative stress marker in STZ-diabetic nephropathy rats by decreasing the renal MDA that correlated with increasing the antioxidant enzymatic activities. However, TMZ did not affect the high blood glucose level. This provides a support for the effect of TMZ in attenuation of microalbuminuria that may be linked to their antioxidant activity independent on the anti hyperglycemic effect (44, 45). The antioxidant activity of TMZ had been evidenced previously by Belardinelli et al., (13) who reported that TMZ decreases plasma levels of free radicals in conditions of high oxidative stress, such as diabetes mellitus. Moreover, long-term administration of TMZ significantly reduced superoxide anions generation and MDA after renal ischemia (46) and myocardial ischemia (47). In vivo, pretreatment with TMZ significantly decreases membrane MDA content of red blood cells incubated with superoxide dismutase inhibitor diethyldithi-

ocarbamate (48). Other in vitro studies have confirmed the antioxidant effect of TMZ (11,49). In human, plasma levels of MDA were decreased after pre-treatment with TMZ during coronary artery by pass surgery (50, 51). So, TMZ seems to be particularly efficient as a free radical scavenger.

In conclusion, the results of the present study demonstrate that TMZ ameliorates oxidative stress and improves renal function in STZ-diabetic nephropathy rats. The improvement of diabetic nephropathy induced by TMZ may have potential therapeutic and prognostic implications clinically.

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الملخص العربي

تأثير دواء "تراي ميتازيدين" على الجهد الأوكسيدي في الفران المصابة بالاعتلال الكلوي السكري

بحث مقدم من:

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أجرى هذا البحث لدراسة تأثير تراي ميتازيدين على الجهد الأوكسيدي في الاعتلال الكلوي السكري والمحدث معمليا بحقن الفران بمادة الأستريزتوتوسين. وقد اجريت الدراسة على ٤٨ فأرا تم تقسيمهم الى مجموعتين أساسيتين المجموعة الاولى استخدمت كمجموعة ضابطة والمجموعة الثانية مصابة بالسكر عن طريق الحقن بمادة الأستريزتوتوسين وقسمت كل مجموعة الى ٣ مجموعات فرعية (مكونة من ٨ فران) مجموعة غير معالجة ومجموعة عولجت بالكابتوبريل وأخرى بالتراي ميتازيدين يوميا لمدة ١٢ أسبوع وفي نهاية المدة تم قياس نسبة الألبومين في البول لمدة ٢٤ ساعة ثم ذبحت الفران وتم فصل المصل لقياس كلا من مستوى الكرياتينين والسكر كما تم وزن الكلى ومقارنته بوزن الجسم ثم قياس مستوى الشقوق الحرة والأنزيمات المضادة للأكسدة في انسجة الكلى. وكانت النتائج انه لوحظ ارتفاع نسبة الألبومين في البول والسكر والكرياتينين في الدم كما زاد وزن الكلى ومستوى الشقوق الحرة فيها مصاحبا لث نقص في مستوى مضادات الأكسدة في الفران المصابة بالاعتلال الكلوي السكري وعندما عولجت بكلا من التراي ميتازيدين أو الكابتوبريل أظهرت تحسن ذو دلالة احصائية واضحة ومن هنا نستنتج أنه يمكن استخدام التراي ميتازيدين كمضاد للأكسدة في علاج الاعتلال الكلوي السكري.

