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Thiamine pyrophosphate improved vascular complications of diabetes in rats with type 2 diabetes by reducing glycation, oxidative stress, and inflammation markers

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Abstract

Background: Thiamine deficiency contributes to hyperglycemia and diabetes complications. Thus, in this study, the effect of thiamine pyrophosphate (TPP) on the in vivo and in vitro formation of glycation, oxidative stress, and inflammatory markers (the main contributors of vascular diabetes complications) was examined in type 2 diabetes rat model.

Methods: Type 2 diabetes was induced in rats with a combination of streptozotocin and nicotinamide (55+200 mg/kg). Two groups of rats, healthy and diabetic, were treated with 0.1% TPP in drinking water daily for 3 months and the 2 others received water only. The glucose, insulin, early to end glycation products, the activity of glyoxalase system, lipid profile, LDL oxidation markers, inflammatory markers, creatinine in the serum, and proteinuria in the urine of all rats were determined. Moreover, albumin and LDL were incubated with glucose in the presence and absence of TPP, and the samples were investigated for glycation and oxidation products. Different variables in all 4 groups were compared with multiple analysis of variance (MANOVA-Tukey) test using SPSS version 16. Significance level was set at $p<0.05$.

Results: TPP decreased the formation of diverse glycation and oxidation products in both in vivo (glycated LDL= 144.50±3.48 and oxidized LDL= 54.08±2.67 µmol/l) and in vitro (glycated LDL= 107.00±2.82 and oxidized LDL= 50.83±1.22 µmol/l). In addition, the vitamin reduced fasting blood sugar (9.23±0.29), insulin resistance (9.10±0.50), tumor necrosis factor-α (285.43±15.97), interleukin-6 (257.65±13.06), and improved the lipid profile, the activity of Glo system (Glo-I= 31.65±1.06 and Glo-II= 27.01±0.90 U/mL) and renal function in the diabetic rat ($p<0.001$).

Conclusion: TPP decreased the major risk factors for diabetic complications and corrected the alternations of glucose and lipid metabolism in type 2 diabetic rats; thus, it is recommended for diabetes treatment.

Keywords: Type 2 diabetes, Glycation, Oxidative stress, Inflammation, Streptozotocin, Diabetic vascular complications, Glyoxalase system, Proteinuria

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Introduction

Type 2 diabetes mellitus is one of the most common diseases in the world that causes serious health and economic challenges. Hyperglycemia causes vascular diabetes complications owing to the induction of glycation, oxidative

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↑What is "already known" in this topic:
Hyperglycemia causes vascular diabetes complications owing to the induction of glycation, oxidative stress, and inflammation. Moreover, atherosclerosis and nephropathy are the main cause of death in these patients. thiamine deficiency leads to hyperglycemia and diabetes complications.

→What this article adds:
We suggested that thiamine pyrophosphate as an active form of the vitamin reduces glycation, oxidative stress, and inflammation markers as cardinal risk factors of vascular complications. Further, we proposed the vitamin improved activity of glyoxalase system, renal function and insulin sensitivity.

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stress, and inflammation (1). Moreover, atherosclerosis and nephropathy are the main causes of death in these patients (2).

Glycation products are the cardinal mediators of insulin resistance, β cell failure, and diabetes disorders (3). Glycated LDL (g-LDL) and its oxidized form (Ox-LDL) contribute to the initiation and progression of atherosclerosis (4). The production of toxic carbonyl active species, such as glioxal (GO) and methylglyoxal (MGO), which is one of the consequences of oxidation of lipids and sugars, leads to carbonyl stress. Furthermore, this phenomenon is responsible for the activation of a series of inflammatory responses leading to accelerated vascular damage in diabetes (5). Glyoxalase system is the most potent enzymatic system for the prevention and reduction of carbonyl stress (6).

Thiamine is an antioxidant and a vital cofactor in the carbohydrate metabolism. Also, thiamine deficiency leads to hyperglycemia and diabetes complications (7). In this study, the effect of thiamine pyrophosphate (TPP) on glycemic, oxidative and inflammatory stress, as major risk factors for vascular disorders in diabetic rats, was studied. Also, the effect of treatment on the production of low glycemic and oxidized albumin and lipoprotein products in vitro was also investigated.

Methods

Materials

All materials were in analytical grade and purchased from Sigma or Merck Chemical Companies.

In vivo studies

Animal model of type 2 diabetes

Eight weeks old male Wistar rats, weighing 180±15, were purchased from the Pasteur Institute, Karaj, Iran. Animals were housed under controlled temperature conditions with a 12-hour light and 12-hour dark cycle, with free access to food and water. After 2 weeks, they were divided into 2 main groups. After a 12-hour fasting, type 2 diabetes was induced in group 1 by single intraperitoneally (i.p.) injection nicotinamide (210 mg/kg body weight in the Na-citrate buffer, pH 4.5) and streptozotocin (55 mg/kg body weight in the citrate buffer, 15 min later) (8).

After 3 days, animals with fasting blood sugar of (FBS) > 11 mmol/L were considered diabetic. Then, each of the 2 main (diabetic and normal) groups was divided into 2 subgroups, with 10 rats in each: subgroup 1: D (for the diabetic group) and N (for the control group), with no more treatments; subgroups 2: D (TPP) and N (TPP) received 0.1% thiamine pyrophosphate (TPP) in drinking water daily for 3 months. The dose of thiamine was selected according to the literature (9) and the authors' experience.

All groups fed on a standard chow diet. The experimental protocol was approved by the Animal Ethical Committee in accordance with the guidelines for the care and use of laboratory animals prepared by Ardabil University of Medical Sciences.

At the end of the experiment, after a 16-hour fast, rats were anesthetized with an i.p injection of ketamine - xylosine (90+10 mg/kg body mass). Then, a blood sample was collected from their heart and transferred into the test tubes with and without EDTA. Serum samples were prepared by 15-minute centrifugation of blood at 5000×g and were stored at −70°C for measurements. Their kidneys were dissected and weighted promptly. The kidney weight index was calculated by dividing kidney weight to rats' body weight.

Determining biochemical parameters

Fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), LDL, HDL, serum creatinine (Cr), and protein excretion in urine (PU) were measured by photometric methods. Moreover, the atherogenic index was computed with LDL/HDL ratio. The serum insulin level was determined by the enzyme-linked immunosorbent assay (ELISA) method using a rat insulin kit (Mercodia, Uppsala, Sweden) and HOMA-IR (homeostasis model assessment of insulin resistance) was calculated as explained previously (4).

Determining glycated products

Glycated albumin (g-Alb) was quantified by a colorimetric method using nitroblue tetrazolium chloride (10). Glycated LDL was determined by the reaction of extracting LDL with oxalic acid and thiobarbituric acid to yield the hydroxymethylfurfuraldehyde chromogen (11, 12). Glyoxal (GO) and methylglyoxal (MGO) were assayed by a reverse phase HPLC (10). The fluorescent AGEs were determined in the serum of rats (4).

Determining oxidative stress markers

Conjugated dienes (CD) in LDL lipids, as early products of LDL oxidation, was analyzed spectrometrically at 234 nm. The molar extinction coefficient of CD is 2.95×10^4 M^{-1} and the results were presented as μM. Fluorescence intensity of end oxidation product of LDL, named oxidation fluorescent product (OFP), was recorded at the emission maximum 430 nm upon excitation at 360 nm (10).

Advanced oxidation protein products (AOPP) was determined based on the spectrophotometric detection, according to the method of Witko-Sarsat et al, as described in our recent papers (4, 13). Levels of malondialdehyde (MDA) and glutathione (GSH) were determined with a commercial assay kit (Cayman Chemical Co., Ann Arbor, MI).

Determining inflammatory markers

Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were determined using ELISA kits (Immunotech, France).

Enzymatic assay

The activity of GLO-1in hemolysate was determined by measuring the initial rate of S-D-lactoylglutathione formation, while the rate of its hydrolysis was a measure of the activity of GLO-2 in all samples and expressed as unit/mL (10, 14).

In vitro albumin and LDL glycation and oxidation

Albumin extraction and glycation

Rat serum albumin (RSA) was extracted and incubated with glucose in the absence and presence of TPP (100

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mg/L). The extraction and incubation procedures were similar to what was explained previously (4).

Determining various glycated products of albumin

All measurements were done at least 3 times, and in case of incompatibility, the experiment was repeated. The g-Alb, MGO, GO, and fluorescent AGEs in the tubes containing the reaction mixtures were measured using the methods explained in the in vivo section.

Purification and formation of glyco-oxidation products of LDL

LDL was isolated with heparin and incubated in the presence and absence of glucose and TPP (100 mg/L). The complete procedure of the study was similar to that we explained before in this article (4).

Determining glycated and oxidized LDL products

The glycated and oxidized LDL products were measured using the methods explained in the in vivo section.

Statistical analysis

All data were expressed as mean±S.D (standard deviations). Different variables in all 4 groups were compared with one-way multiple analysis of variance (MANOVA-Tukey) test using SPSS version 16. Significance level was set at $p<0.05$.

Results

The results of the in vivo experiment

The levels of fasting blood sugar, insulin, HOMA-IR, lipid profile, and kidney function tests in the rat groups are represented in Table 1. FBS, HOMA index, as a marker of insulin resistance, TG, TC, LDL, and the atherogenic index increased significantly in the diabetic rats compared to the healthy group (Table 1). Thiamine pyrophosphate significantly reduced the parameters in diabetic rats. The treatment decreased the levels of TG, TC, and the atherogenic

Table 1. The effect of thiamine pyrophosphate (TPP) on fasting blood sugar, insulin, HOMA-IR, and glycation products of the healthy and diabetic rats

Variable	Groups				p
	N	N (PLP+THC)	D	D (PLP+THC)	< 0.001
Blood sugar (mmol/L)	4.50 ± 0.27	4.45± 0.27	15.73 ± 0.46^{N}	9.23 ± 0.29$^{N, D}$	< 0.001
Insulin (µU/mL)	17.04 ± 0.90	16.97± 0.87	13.03 ± 0.71^{N}	11.72 ± 0.34$^{N, D}$	< 0.001
HOMA-IR	3.40 ± 0.427	3.35 ± 0.24	9.10 ± 0.50^{N}	4.80± 0.20$^{N, D}$	< 0.001
Triglyceride (mmol/L)	0.92 ± 0.02	0.88 ± 0.02$^{N, D}$	3.10 ± 0.16^{N}	1.81 ± 0.08$^{N, D}$	< 0.001
Total cholesterol (mmol/L)	2.66 ± 0.07	2.35 ± 0.08$^{N, D}$	4.33 ± 0.24^{N}	3.45 ± 0.18$^{N, D}$	< 0.001
HDL (mmol/L)	1.31 ± 0.06	1.27 ± 0.05	0.48 ± 0.01^{N}	1.00 ± 0.03$^{N, D}$	< 0.001
LDL (mmol/L)	0.58± 0.01	0.53 ± 0.02	2.61 ± 0.24^{N}	1.53 ± 0.16$^{N, D}$	< 0.001
HDL/LDL	0.44 ± 0.01	0.41 ± 0.01$^{N, D}$	5.43 ± 0.49^{N}	1.53 ± 0.11$^{N, D}$	< 0.001
Creatinine (µmol/L)	59.65±3.87	65.70±4.29	105.73 ± 6.53^{N}	83.08 ± 5.09$^{N, D}$	< 0.001
Proteinuria (mg/24 h)	11.73 ± 0.95	9.35 ± 0.81	320.62 ± 17.63^{N}	65.25 ± 3.92$^{N, D}$	< 0.001
Kidney weight index	0.77 ± 0.05	0.75 ± 0.04	1.350.77±0.71^{N}	0.81±0.05^{D}	< 0.001

^{N} indicates significance of data comparing group N (normal) with other groups
^{D} indicates significance of data comparing group D (diabetic) with other groups

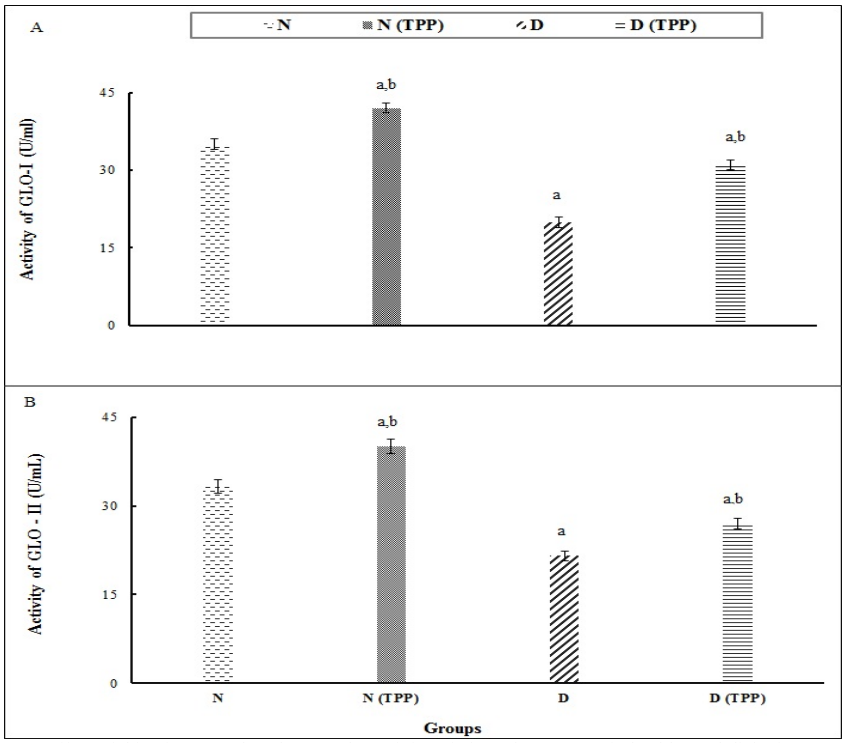

Fig. 1. Effect of thiamine pyrophosphate on the activity of glyoxalase system in healthy and diabetic rats: (A) Activity of glyoxalase-I; (B) Activity of glyoxalase-II.
[a] indicates significance of data comparing the healthy group (N) with other groups ($p<0.001$).
[b] indicates significance of data comparing group diabetic (D) with other groups ($p<0.001$).

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index in the treated healthy rats compared to untreated rats ($p<0.001$).

Glyoxalase-I and II activities in treated and untreated rat groups are presented in Figure 1. Diabetes induction in rats decreased the activity of Glo system, but the vitamin induced the activity of Glo-I and Glo-II in the healthy and diabetic rats ($p<0.001$).

Comparison of the effect of the treatment on glycation (g-Alb, g-LDL, GO, MGO, and AGES), oxidative stress (early and end oxidation products of LDL, AOPP, MDA, and GSH), and inflammatory (TNF-α and IL-6) markers in the named groups is represented in Table 2. Levels of glycation, oxidative stress, and inflammatory markers decreased in the treated diabetic rats than in the untreated, but GSH level was higher in the treated than in the untreated diabetic rats ($p<0001$). Furthermore, the levels of the glycation and inflammatory markers were lower in the healthy rats compared to the untreated rats ($p<0.001$).

The results of the in vitro study

The effects of TPP on the in vitro formation of various glycation products (early to end) of RSA and LDL glycation and oxidation (early and end) products are presented in Table 3. The vitamin diminished the levels of early (g-Alb), intermediate (GO and MG), and end products (AGEs) of glycation as well as LDL glycation and oxidation products.

Discussion

The effect of thiamine pyrophosphate on the activity of the glyoxalase system, various glycation products (early to end), oxidative stress markers, as early and end oxidation products of LDL, as well as advanced oxidation protein products (AOPP) has not been explored in rats with type 2 diabetes. In this study, thiamine pyrophosphate reduced various glycation, oxidative stress, and inflammatory markers, as risk factors of vascular diabetes complications, in rats with type 2 diabetes. Moreover, the treatment showed a beneficial effect on glucose metabolism, lipid profile, glyoxalase system activity, and kidney function. Also, in vitro inhibitory property of the vitamin on the diverse glycation and oxidation products of albumin and LDL was observed.

Diabetes and thiamine deficiency reduce the activity of the glutoxylase system. TPP decreased blood glucose along with improving insulin action in the diabetic rats. Insulin and HOMA-IR levels were, respectively, higher and lower ($p<0.001$) in treated diabetic rats than in the untreated group (Table 1). Thiamine is necessary for insulin synthesis and secretion (15). In the thiamine-deficient state, glucose undergoes metabolism via alternate pathways, which can result in insulin resistance and complications (16). The glyoxalase system decreases dicarbonyl compounds and AGEs (17). Diabetes and deficiency of thiamine reduce the activity of Glo system. Moreover, thiamine deficiency is common in diabetes (4, 10). Various glycation products, including glycated albumin, dicarbonyl compounds, and AGEs, have been known as the sources of oxidative stress and inflammatory markers that induce insulin-resistance, hypertension, neurodegenerative disease, and diabetic vascular complications (18, 19). AGEs may interfere in the insulinsecretion (20). Prerhaps, AGEs were involved in the pathogenesis of insulin resistance and accelerated atherosclerosis in diabetes through the induction of oxidative stress and inflammation (21). In this study, TPP, as a potent

Table 2. Effect of thiamine pyrophosphate (TPP) on the lipid profile of healthy and diabetic rats

Variable	Groups				p
	N	N (TPP)	D	D (TPP)	
Glycated albumin (µmol/L)	110.65 ± 6.60	85.71 ± 5.40$^{N, D}$	394.63 ± 16.65^{N}	291.00 ± 14.40$^{N, D}$	< 0.001
Glycated LDL (µmol/L)	51.13 ± 1.70	38.06 ± 0.85$^{N, D}$	185.90 ± 6.77^{N}	144.50 ± 3.48$^{N, D}$	< 0.001
Glyoxal (µmol/L)	19.66 ± 0.91	9.82 ± 0.88$^{N, D}$	121.70 ± 6.40^{N}	52.38 ± 2.65$^{N, D}$	< 0.001
Methylglyoxal (µmol/L)	20.01 ± 0.97	10.37 ± 0.90$^{N, D}$	139.21 ± 5.10^{N}	47.51 ± 2.37$^{N, D}$	< 0.001
AGEs (FI, A.U)	52.07 ± 3.65	37.94 ± 2.48$^{N, D}$	292.30 ± 13.67^{N}	160.45 ± 7.06$^{N, D}$	< 0.001
CD (µmol/L)	16.13±0.90	15.02±0.63	107.96 ± 4.83^{N}	54.08 ± 2.67$^{N, D}$	< 0.001
FOP (µmol/L)	233.73 ± 14.40	220.33 ± 11.71	510.93 ± 22.73^{N}	330.55 ± 18.92$^{N, D}$	< 0.001
AOPP (µmol/L)	24.57 ± 0.99	18.85 ± 0.86	79.84±5.01^{N}	37.27±2.89$^{N, D}$	< 0.001
MDA (µmol/L)	10.58± 1.31	8.53 ± 0.92	157.61 ± 7.24^{N}	77.53 ± 4.16$^{N, D}$	< 0.001
GSH (µmol/L)	175.58± 8.31	188.67 ± 9.01	88.43 ± 3.97^{N}	145.61± 8.31$^{N, D}$	< 0.001
TNF-α (µmol/L)	120.54± 7.31	90.67 ± 5.01$^{N, D}$	285.43 ± 15.97^{N}	200.61± 8.31$^{N, D}$	< 0.001
Il-6 (µmol/L)	86.58±4.28	57.67 ± 2.31$^{N, D}$	257.65 ± 13.06^{N}	163.89± 6.35$^{N, D}$	< 0.001

^{N} indicates significance of data comparing group N with other groups ($p<0.001$)
^{D} indicates significance of data comparing group D with other groups ($p<0.001$)

Table 3. The effect of thiamine pyrophosphate (TPP) on the in vitro formation of various glycated products of rat serum albumin (RSA)

		Tube Content	Rat serum albumin glycation products			
			Glycated albumin (µmol/L)	Methylglyoxal (µmol/L)	Glyoxal (µmol/L)	AGEs (AU)
In vitro	Albumin	RSA	111.70±3.40	9.78±0.10	6.05±0.08	111.70±3.40
		RSA+ Glc	987.47±9.31	33.05±0.51	18.85±0.21	987.47±9.31
		RSA+ Glc + TPP	425.42±4.82	17.88±0.25	10.30±0.17	425.42±4.82
		Tube Content	LDL glycation and oxidation products			
			Glycated LDL (µmol/L)	Early oxidation products (µmol/L)	End Oxidation products (AU)	
	LDL	LDL	20.10±0.80	17.01±0.62	15.17±0.44	
		LDL+ Glc	317.45±7.07	129.76±2.55	476.01±10.84	
		LDL+ Glc + TPP	107.00±2.82	50.83±1.22	110.01±2.36	

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antiglycating compound, induced the activities of glyoxalase-1 and glyoxalase-2 (Fig. 1. A and 1.B) and decreased the early (g-Alb and g-LDL), intermediate (GO and MGO), and end glycation products (AGEs) in the treated healthy and diabetic rats (Table 2) ($p<0.001$). Further, the vitamin has in vitro antiglycating activity on diverse glycation products (Table 3). Based on the literature review, the effect of TPP on the Glo system activity in diabetes has not yet been investigated. The reducing effect of thiamine on the formation of AGEs in vitro and in vivo as well as MGO formation in the in vitro were presented (22, 23). However, the effects of thiamine on different glycation products in vivo and in vitro was investigated. Thiamine may reduce different glycation products with antioxidant property, dicarbonyl scavenger, and activation of the Glo system (24).

Oxidative stress and inflammation stimulate insulin resistance and diabetes complications (25). Thus, the treatment decreased insulin resistance and intercepted atherosclerosis over and above amended nephropathy in the diabetic rats because of reducing oxidative stress. Over and above the treatment decreased advanced oxidation protein products and malondialdehyde, along with the elevation of glutathione level. Further, it abstracted TNF-α and IL-6 as inflammatory markers (Table 2). Previously, the anti-inflammatory effect of thiamine with reduction of cited inflammatory markers was reported in a chronic model of inflammation in the rat (26).

The rising levels of TG, LDL, and VLDL, along with a reduction of HDL, were observed in diabetic nephropathy, diabetic microalbuminuria, and thiamine deficiency (27, 28). The treatment had a positive effect on the lipid profile in the healthy and diabetic rats (Table 1). The treatment decreased TG, TC, and the atherogenic index in the healthy and diabetic rats but reduced LDL only in the diabetic rats ($p<0.001$). Thiamine reduces lipogenesis in the liver and adipose tissue in glycemic condition (29).

Glycated LDL is more sensitive to oxidation than the nonglycated of LDL. Oxidized LDL has a principal role in the initiation and progression of atherosclerosis (30). Glycation and oxidation of LDL increase following glycemia, dyslipidemia, oxidative stress, and glycation (31, 32). The results of this study revealed an inhibitory effect of TPP on the glycation and oxidation of LDL in both conditions, in vivo ($p<0.001$) and in vitro (Tables 2 and 3) for the first time. The treatments that inhibit the formation of the end oxidation products of LDL can prevent the formation of any atheromatous lesions (4, 10).

Diabetic nephropathy (DN) contributes to renal failure. Diabetes induction elevated urinary protein excretion, serum creatinine, and kidney weight index in the rats (Table 1). Moreover, a negative correlation was found between kidney weight index and renal function (4). The vitamin reduced the levels of kidney function markers in the diabetic rats ($p<0.001$). Furthermore, no difference was observed between kidney weight index in the treated diabetic rats and the healthy rats. Level of g-Alb is a better predictor of DN progression than glycated hemoglobin in humans with type 2 diabetes (33). Moreover, AGEs have a cardinal role in the progression of vascular dysfunction due to induction of oxidative stress and inflammation (34). Proinflammatory cytokines, as TNF-α and IL-6, contribute to renal lesions through cellular injury, alteration of the glomerular protein permeability barrier, and development of intracranial inflammatory damage which lead to diabetic nephropathy (35). TPP improved kidney dysfunction in diabetic rats by reducing glycation, protein, lipid oxidation, and inflammatory markers (Table 2). In accordance with the results of the present study, there is some evidence that indicate the increase in glycated albumin, MGO, and AGEs and the decrease in the activity of Glo-1 are associated with nephropathy (4, 10). In this study, for the first time, the healing effect of thiamine pyrophosphate on renal impairment in type 2 diabetic rats was reported.

Conclusion

Thiamine pyrophosphate improves vascular diabetes complications by the loweing effect on glycation, oxidative stress, and inflammation markers and by an advantageous effect on insulin action, the activity of glyoxalase system, and lipid profile in the diabetic rats.

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Conflict of Interests

The authors declare that they have no competing interests.

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