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The Effect of Coenzyme Q10 on Oxidative Stress and Endoplasmic Reticulum Stress in an Experimental Diabetes Model

Toprak MS*[1], Sonmez D[2], Kaleler I[2], Usak ST[2], Kucukhuseyin O[2], Zeynep Gungor[1], Ilhan Yaylim[2] and Huseyin Sonmez[1]

[1]Department of Medical Biochemistry, Istanbul University Cerrahpasa, Turkey

[2]Department of Molecular Medicine, Istanbul University, Turkey

*Corresponding author: Muhammet Sait Toprak, Department of Medical Biochemistry, Cerrahpasa Medical School, Istanbul University Cerrahpasa, Istanbul, Turkey, Tel: +905304036556; Email: msaittoprakk@gmail.com

Abstract

Diabetes is the 8th leading cause of death worldwide. The greatest increase in rates has been seen in low and middle-income countries. Urbanization and lifestyle changes such as an increase in sedentary lifestyles, increase in the intake of foods with high energy but poor nutrition levels have caused a high incidence of the disease worldwide. Treating the mechanisms involved in the pathogenesis of diabetes with nutrients such as antioxidants can reduce further complications of the disease. This study tests whether hyperglycemia triggers endoplasmic reticulum stress in the liver and brain tissues of rats and the possible role of oxidative stress in this pathway. We investigated the relationship between oxidative and endoplasmic reticulum stress via the TWEAK pathway, and how the coenzyme Q10 affects further diabetic complications. We examined oxidative stress markers (Oxidized Glutathione, Reduced Glutathione) in the liver and brain tissues of rats in the control, diabetic, and diabetic antioxidant groups by ELISA method. We also determined endoplasmic reticulum stress markers (PERK, ATF6, GRP78) and the TWEAK molecule by the Western Blott method in the same experimental groups. Our results underlined that coenzyme Q10 had a significant and positive effect on oxidative and endoplasmic reticulum stress parameters, and TWEAK levels. We also found a more robust positive correlation between oxidative and endoplasmic reticulum stress parameters for the liver compared to the brain. However, a significant positive correlation was also seen between TWEAK and endoplasmic reticulum stress of the brain.

Keywords: Diabetes Mellitus; Oxidative Stress; Endoplasmic Reticulum Stress; Coenzyme Q10; Tweak

Abbreviations: PERK: Protein Kinase RNA-Like ER Kinase; ATF6: Activating Transcription Factor 6; IRE1: Inositol-Requiring Kinase 1; UPR: Unfolded Protein Response.

Introduction

Diabetes Mellitus is a multifactorial disease characterized by hyperglycemia resulting from deficiencies in insulin production or activity [1,2]. According to the data of the International Diabetes Federation, while there were 285 million diabetes patients in 2010 and 425 million in 2017 in the world, the estimated expectation for 2045 is 629 million people. According to 2017 data, 4 million people die every year due to diabetes complications worldwide [3].

Several different mechanisms such as oxidative stress, inflammation, and endoplasmic reticulum stress play an important role in the pathogenesis of diabetes [4-

6]. In recent years, conducted studies have shown that endoplasmic reticulum stress plays an important role in the loss of function of pancreatic beta cells and the development of insulin resistance. Endoplasmic reticulum stress is the excessive accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum that occurs in various physiological or pathological conditions where the capacity of the endoplasmic reticulum is exceeded [7-10]. Intracellular signaling pathways called unfolded protein response (UPR) are activated to restore this disturbed balance in the cell and to get rid of the stress with minimum damage [1].

Protein kinase RNA-like ER kinase (PERK), Activating transcription factor 6 (ATF6) and Inositol-requiring kinase 1 (IRE1) proteins play a role in UPR signaling pathways. Under normal conditions, PERK, ATF6, and IRE1 proteins, which co-exist with the "glucose regulatory protein" (GRP78) and remain in an inactive state, become active by separating from GRP78 when stress exceeding the endoplasmic reticulum capacity is encountered [1]. Active UPR signaling pathways are responsible for restoring homeostasis of proper production, processing, and folding of proteins. They also reduce the protein load of the endoplasmic reticulum by stopping protein translation. GRP78 also helps to reduce endoplasmic reticulum stress by both adhering to misfolded proteins and helping to prevent misfolding during translocation in the endoplasmic reticulum [10].

Under conditions of prolonged and severe endoplasmic reticulum stress, the UPR is unable to maintain normal cellular functions and consequently cell death usually caused by apoptosis is triggered [1,6,11]. Increased cell death leads to loss of tissue function and causes various diseases related to endoplasmic reticulum stress [12-15]. Apoptosis is thought to be the most important cause of pancreatic beta-cell loss, especially in type I and type II diabetes patients [16,17].

TWEAK (TNF-like weak apoptosis inducer) is a member of the TNF family, which has been suggested to have a proapoptotic effect in various cells [18]. TWEAK binds to its receptor called Fn14 under various pathological conditions and stimulates many mechanisms including cellular growth, proliferation, migration, differentiation, apoptosis, angiogenesis, fibrogenesis, and inflammation. Although there are studies suggesting that there may be a relationship between TWEAK and endoplasmic reticulum stress, there is yet no study that completely explains the mechanism [19,20].

Oxidative stress occurs with the disruption of the balance between free radicals accumulating in the body and antioxidant defense systems [21]. Oxidative stress causes serious damage to pancreatic β cells and has an important role in the pathogenesis of diabetes [22,23]. Glutathione is one of the endogenous antioxidants that play a major role in reducing the oxidative stress which increases in the development of diabetes [24]. The ratio between the oxidized (GSSG) and reduced (GSH) forms of glutathione is used as one of the most important indicators of oxidative stress [25].

Coenzyme Q10 is a vitamin-like quinone found at high levels in various tissues. Coenzyme Q10 is also a very powerful antioxidant and plays an important role in protecting cells from the effects of oxidative stress. Studies indicate that patients with diabetes have significantly lower plasma coenzyme Q10 levels compared to normal healthy individuals. It has been suggested that exogenous supplementation of coenzyme Q10 potentially attenuates mitochondrial dysfunction induced by oxidative stress, thereby improving glycemic control in type II diabetes [26-29]. In addition, recent experimental studies link insulin resistance to a decrease in coenzyme Q10 expression and show that supplementation with coenzyme Q10 can restore insulin sensitivity [30].

In this study, we aimed to examine whether hyperglycemia triggers endoplasmic reticulum stress in the liver and brain tissues, how the possible relationship with oxidative stress develops in this mechanism, and whether a powerful antioxidant coenzyme Q10 reduces endoplasmic reticulum stress in rats in a streptozotocin (STZ)-induced experimental diabetes model. In addition, we aimed to examine the possible connections of the TWEAK molecule with the UPR signaling pathways and to examine whether there is a relationship between them and endoplasmic reticulum stress.

Materials and Methods

Experimental Animals

The experimental protocol was approved by the Bezmialem Experimental Animals Local Ethics Committee. The experiment was carried out on 24 healthy adult male Sprague Dawley rats weighing 300-350 g. Rats were housed in polypropylene cages, maintained under standardized conditions (12 h light/dark cycle, 24°C, 35–60% humidity), and allowed free access to diet and purified drinking water ad libitum.

Experimental Design

Rats were randomly divided into three groups each consisting of eight animals. Group I: Control rats (distilled water 10 ml/kg), Group II: Diabetic rats, Group III: Diabetic rats treated with 10 mg/kg coenzyme Q10 (1% aqueous solution of Tween 80). An experimental diabetes model was developed by administering a single dose of 65 mg/

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kg STZ solution (dissolved in citrate buffer, pH 4.5) (cat no. ab142155, Abcam, Cambridge, UK) intraperitoneally to rats in the diabetes and diabetic antioxidant group (31). Hyperglycemia was confirmed by elevated blood glucose levels at 72 h after injection. The animals with fasting blood glucose levels greater than 200 mg/dl were considered diabetic [31,32]. The diabetic antioxidant group rats were administered 10 mg/kg "coenzymeQ10" (cat no. ab143173, Abcam, Cambridge, UK) intraperitoneally for 42 days [32]. Body weights and fasting blood glucose levels of the rats were measured regularly. At the end of the experiments, anesthesia was performed with 2% isoflurane inhalation [33,34]. Blood taken from the tail veins of rats was stored at -80°C for ELISA studies. Liver and brain tissues from rats were stored at -80°C for Western Blot studies.

Western Blotting

The protein expressions of the endoplasmic reticulum stress proteins GRP78, ATF6, PERK, and the apoptotic marker TWEAK were assessed by western blotting analysis. Protein isolation from liver and brain tissues was performed with "Mammalian cell extraction kit (cat no. ab65399, Abcam, Cambridge, UK)". The isolation buffer was prepared with "Extraction buffer - DTT - protease" chemicals as specified in the kit protocol. Tissues were homogenized in ice with this isolation buffer. Protein levels in the resulting homogenates were determined with the BCA kit (cat no. 21071, Intron Biotechnology Inc., S. Korea).

The procedure of western blotting was performed according to the protocol of Marie, et al. [35]. The proteins were separated by SDS-PAGE. Then proteins are transferred to the PVDF membrane. Membranes were probed by primary antibodies overnight at 4 °C. The primary antibodies were used as follows: anti-ATF6 (cat no. ab203119, Abcam, Cambridge, UK) diluted at 1:1000; anti-GRP78 (cat no. ab109659) diluted at 1:2000; anti-PERK (cat no. ab79483) diluted at 1:100; anti-TWEAK (cat no. ab37170) diluted

at 1:1000. Then the membrane was incubated with a secondary antibody (1:2000; ab97069, Abcam, Cambridge, UK) at room temperature for 1 h. GAPDH was used as an internal control. The protein bands were visualized with Enhanced Chemiluminescence (ECL) (cat no. K22030, Abbkin Superlumia ECL Plus HRP Substrate Kit, USA) and their densitometry was done using Image J software (Total lab software, Wales, UK).

ELISA

GSSG (cat no. E1264Ra, Bioassay, Shanghai) and GSH (cat no. E1443Ra, Bioassay, Shanghai) levels in the blood taken from the tail veins of the rats on the 42nd day were determined by the ELISA method.

Statistical Analysis

Data analysis was conducted using SPSS statistical analysis software (version 20.0; SPSS Inc, Chicago, IL, USA). Results were expressed as means ± SD for continuous variables. ANOVA test was used to show the differences in protein expressions in liver and brain tissues of rats. Comparison of continuous variables of paired groups was done with Student's t-test. Correlations between study variables were analyzed using the Pearson correlation method. p-values less than 0.05 were considered statistically significant.

Results

Effect of Coenzyme Q10 Administration on Body Weight

As illustrated in Table 1, there was no significant difference between the body weight in all groups before the experiment (p=0.428). The body weight of diabetic rats showed a significant decrease after the administration of STZ (p=0.017). The weight loss of rats in the diabetic antioxidant group was less than that of the diabetic rats.

	Initial	21st day	42nd day
Control	296.3 ± 65.4*	327.5 ± 67.5	335.7 ± 57.3
Diabetic	311 ± 45.2*	263.3 ± 34.5	241 ± 29.9**
Coenzyme Q10	297 ± 49.8*	235.3 ± 26.7	243.6 ± 34.4

Table 1: Effect of coenzyme Q10 on body weight.
Values are expressed as mean ± SD; n=8. * p=0.428, ** p=0.017 as compared to initial body weight of diabetic group.

Effect of Coenzyme Q10 Administration on Blood Glucose Levels

Among the diabetic rats, glucose level was significantly increased when compared to control rats (p=0.000). The glucose levels of the rats in diabetic antioxidant group were

found to be statistically significantly lower than those in the diabetic group (p=0.009). Glucose levels of the diabetic antioxidant group at the end of the treatment were found to be statistically significantly lower than on the 21st day of treatment (p=0.001) (Table 2).

	Initial	**21ˢᵗ day**	**42ⁿᵈ day**
Control	94.6 ± 9.8	81.4 ± 5.6	104 ± 8.7
Diabetic	104 ± 8.7	455.6 ± 140.1	496.6 ± 68.3*
Coenzyme Q10	89.7 ± 12.1	536.5 ± 63.1	384.8 ± 93.6** #

Table 2: Effect of coenzyme Q10 on blood glucose levels (mg/dl).
Values are expressed as mean ± SD; n=8. * p=0.000 as compared to control group, ** p=0.009 as compared to diabetic group, # p=0.001 as compared to 21ˢᵗ day of antioxidant group.

	GSH (mg/L)	**GSSG (mg/L)**	**GSH/GSSG ratio**
Control	47.43 ± 14.12	11.54 ± 3.329	4.509 ± 1.951
Diabetic	31.62 ± 13.72*	12.27 ± 3.741#	2.743 ± 1.412*
Coenzyme Q10	57.41 ± 18.99**	9.196 ± 3.847##	7.099 ± 3.625**

Table 3: Oxidative stress parameters.
Values are expressed as mean ± SD; n=8. * $p<0.05$ as compared to control group, ** $p<0.05$ as compared to diabetic group, # p=0.343 as compared to control group, ## p=0.063 as compared to diabetic group

Oxidative Stress Parameters

GSH values and GSH/GSSG ratio; were found to be lower in the diabetic group than in the control group (p=0.019, p=0.028), higher in the diabetic antioxidant group than in the diabetic group (p=0.003, p=0.003) and higher in the diabetic antioxidant group than in the control group (p=0.126, p=0.048). GSSG values were found to be higher in the diabetic group compared to the control group (p=0.343) and to be significantly lower in the diabetic antioxidant group than in the diabetic group and control group (p=0.063, p=0.106) (Table 3).

Brain Tissue Western Blotting Results

TWEAK, GRP78 and ATF6 proteins were found to be statistically significantly higher in the diabetic group than in the control group ($p<0.001$), and PERK is also higher but not significantly so (p=0.158). TWEAK, GRP78, ATF6, and PERK proteins were found to be statistically significantly lower in the diabetic antioxidant group than in the diabetes group ($p<0.01$). TWEAK, PERK, and ATF6 proteins were found to be statistically significantly lower in the diabetic antioxidant group than in the control group ($p<0.05$). GRP78 was found to be statistically significantly higher in the diabetic antioxidant group than in the control group (p=0.005) (Figure 1).
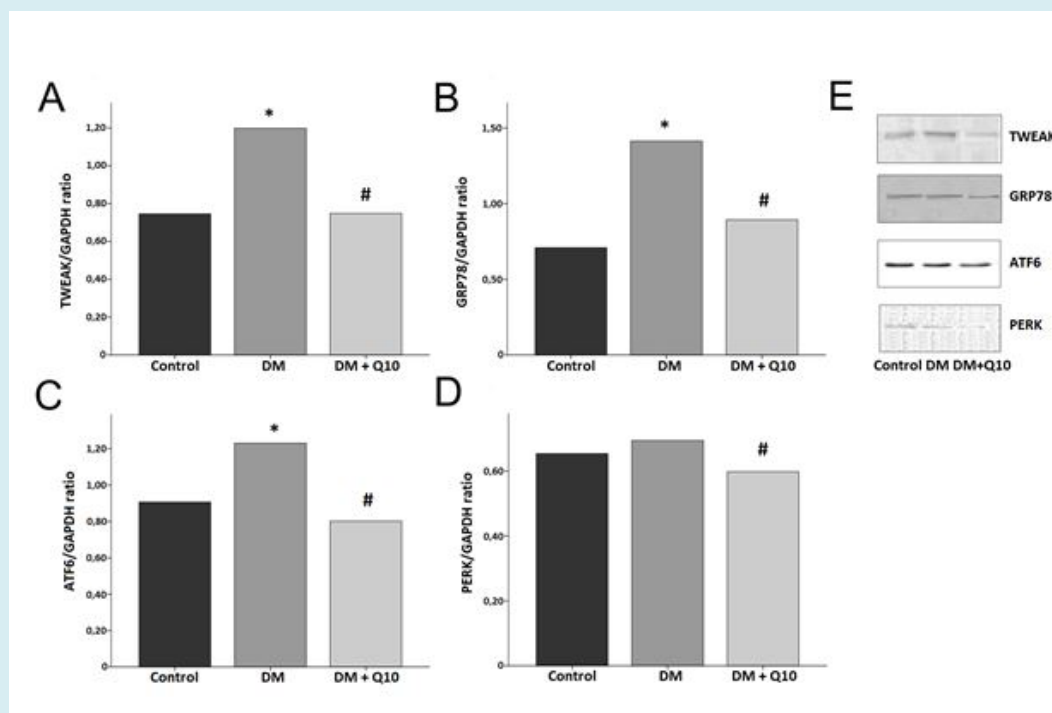

Figure 1: (A-E) The brain protein levels of TWEAK, GRP78, ATF6 and PERK detected by western blotting. The data is expressed as mean ± SD; n=8. * $p<0.001$ versus control group; # $p<0.01$ versus DM group.

When we look at the correlation relationship between continuous variables of endoplasmic reticulum stress in brain tissue in our study, it is observed that there is a statistically significant positive correlation between PERK and GRP78 (r=0.455, p=0.025), between ATF6 and GRP78 (r=0.750, p=0.000), and between ATF6 and PERK (r=0.436, p=0.033) (Table 4).

		TWEAK	GRP78	PERK	ATF6
TWEAK	r	1			
	p	0			
GRP78	r	0.56	1		
	p	**0.004***	0		
PERK	r	0.187	0.455	1	
	p	0.383	**0.025***	0	
ATF6	r	0.622	0.75	0.436	1
	p	**0.001***	**0.000***	**0.033***	0

Table 4: Brain tissue correlation findings.

Correlations between study variables were analyzed using the Pearson correlation method. The r value represents the correlation coefficient and the p value represents the statistical significance value. p-values less than 0.05 were considered statistically significant.

Liver Tissue Western Blotting Results

GRP78 and PERK proteins were found to be statistically significantly higher in the diabetic group than in the control group (p<0.05), and were found to be statistically significantly lower in the diabetic antioxidant group than in the diabetic group (p<0.01). TWEAK and ATF6 proteins were found to be statistically significantly lower in the diabetic group than in the control group (p<0.001), and were found to be statistically significantly higher in the diabetic antioxidant group than in the diabetic group (p<0.01) (Figure 2).
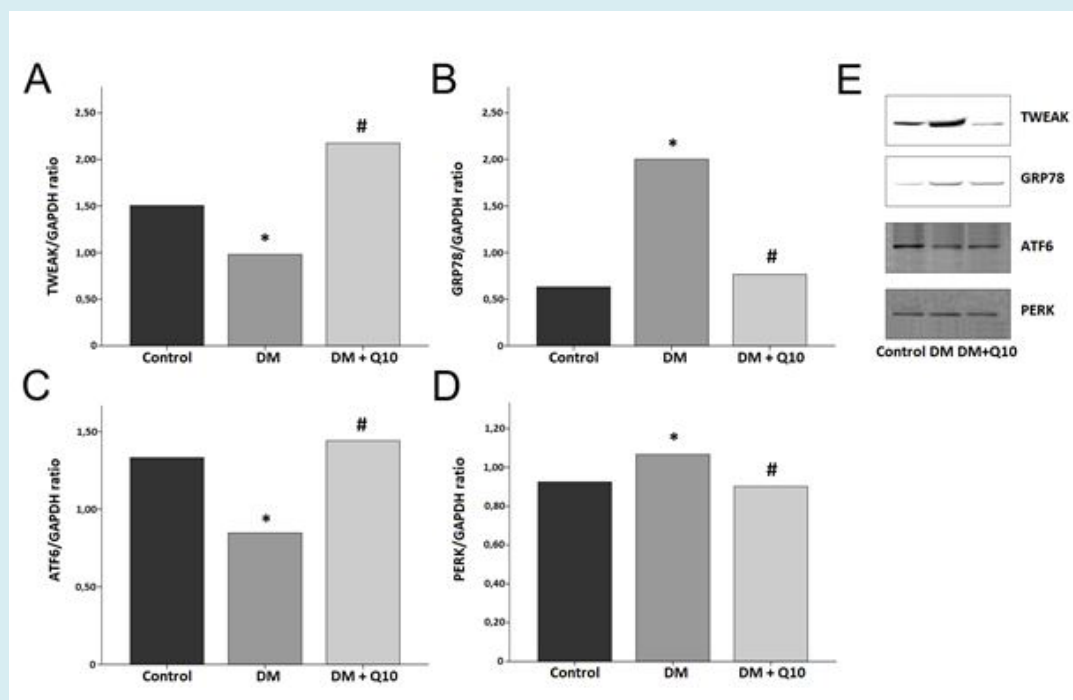

Figure 2: (A-E) The liver protein levels of TWEAK, GRP78, ATF6 and PERK detected by western blotting. The data is expressed as mean ± SD; *, p<0.05 versus control group; #, p<0.01 versus DM group.

When we look at the correlational relationship between continuous variables of endoplasmic reticulum stress in liver tissue in our study, it is seen that there is a positive correlation between ATF6 and TWEAK (r=0.719, p=0.000), a positive correlation between PERK and GRP78 (r=0.588, p=0.003), and a negative correlation between ATF6 and GRP78 (r= -0.470, p=0.020) (Table 5). In addition, when we look at the correlation between oxidative stress parameters and endoplasmic reticulum stress parameters in the liver tissue, there is a negative correlation between GSH and GRP78 (r= -0.476, p=0.019), a negative correlation between GSH and PERK (r= -0.586, p=0.003) (Table 6).

		TWEAK	GRP78	PERK	ATF6
TWEAK	r	1			
	p	0			
GRP78	r	-0.221	1		
	p	0.298	0		
PERK	r	0.027	0.588	1	
	p	0.899	**0.003***	0	
ATF6	r	0.719	-0.47	-0.028	1
	p	**0.000***	**0.020***	0.895	0

Table 5: Liver tissue correlation findings.

Correlations between study variables were analyzed using the Pearson correlation method. The r value represents the correlation coefficient and the p value represents the statistical significance value. p-values less than 0.05 were considered statistically significant.

		TWEAK	GRP78	PERK	ATF6
GSH	r	0.151	-0.476	-0.586	0.343
	p	0.482	**0.019***	**0.003***	0.101
GSSG	r	-0.387	-0.054	-0.136	-0.201
	p	0.062	0.802	0.527	0.347
GSH / GSSG	r	0.37	-0.321	-0.39	0.32
rate	p	0.075	0.127	0.06	0.127

Table 6: Liver tissue correlation findings (oxidative stress and endoplasmic reticulum stress).

Correlations between study variables were analyzed using the Pearson correlation method. The r value represents the correlation coefficient and the p value represents the statistical significance value. p-values less than 0.05 were considered statistically significant.

Discussion

Diabetes mellitus, one of the leading causes of death globally, is a chronic endocrine disease that causes hyperglycemia resulting from deficiencies in insulin production or activity, as well as disruptions in carbohydrate, fat, and protein metabolism [1-3]. Acute and chronic complications, which occur as a result of failure to control hyperglycemia in the advanced stages of diabetes, negatively affect the quality of life of patients and lead to serious organ failure. The most affected organs in diabetes are the pancreas, brain, kidney, and liver [1,36].

Although many different mechanisms play a role in the pathogenesis of diabetes, oxidative stress is one of the conditions that have the most impact on it [4]. Recent studies suggest that endoplasmic reticulum stress has an important effect on the pathogenesis of diabetes too. There are studies showing that endoplasmic reticulum stress triggers diabetes, especially because it accelerates beta cell death, increases insulin deficiency, and causes insulin resistance [37,38]. One of the major causes of endoplasmic reticulum stress is oxidative stress [24]. Oxidative stress, which develops with the increase of the effect of free radicals in the cell, may cause stress development by interacting with redox signal mediators that play a role in the protein folding process in the endoplasmic reticulum lumen [39,40].

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Antioxidant defense systems prevent damage caused by oxidative stress and endoplasmic reticulum stress. Antioxidant molecules are nucleophilic and reductive in nature and react with oxidants which in turn are usually electrophilic, giving them one or two electrons. Coenzyme Q10 acts as an antioxidant and as an indirect stabilizer of calcium channels in the prevention of lipid peroxidation and reduction of calcium overload [41-44].

Based on this, we aimed to investigate whether hyperglycemia in liver and brain tissues triggered endoplasmic reticulum stress in rats by an experimental diabetes mellitus model and reveal whether coenzyme Q10 would have a preventing effect by suppressing oxidative stress. Another aim of our study was to examine the possible functions of the TWEAK molecule in the UPR signaling pathways and its relationship with endoplasmic reticulum stress.

Mohamed et al. administered 20 mg/kg of coenzyme Q10 to diabetic rats for 2 weeks and showed that coenzyme Q10 statistically significantly reduced blood glucose levels [45]. Similarly, in our study, we found that the glucose levels of the rats in the diabetic antioxidant group on the 42nd day of treatment were statistically significantly lower than the diabetic counterpart, same as seen on the 21st day of the treatment. Similar studies conducted by Fatemeh, et al. and Motawi, et al. revealed that coenzyme Q10 statistically significantly reduced glucose levels [46,47]. These studies show that the glucose-lowering effect of coenzyme Q10 occurs by increasing the glucose utilization of cells and suppressing gluconeogenesis in the liver [45-47].

Glutathione is considered the most abundant molecule among the endogenous antioxidants, responsible for preventing the damage caused by oxidative stress in the body. The ratio between the oxidized (GSSG) and reduced (GSH) forms of the glutathione molecule is one of the best indicators of redox and it decreases under oxidative stress conditions [24,25,48].

Maheshwari et al. administered 10 mg/kg coenzyme Q10 to diabetic rats for 42 days. In this study, they showed that coenzyme Q10 statistically significantly reduced malondialdehyde (MDA) levels, which are oxidative stress indicators in the kidney tissue, and statistically significantly increased the levels of superoxide dismutase, catalase, and GSH levels, which are important antioxidants [32]. Another study showed that coenzyme Q10 treatment inhibited lipid peroxidation caused by hyperglycemia and decreased oxidative stress by increasing the activity of antioxidant enzymes such as SOD, catalase, and GSH [49]. Our results are parallel with the studies above.

In our study, we found a positive correlation between oxidative and endoplasmic reticulum stress markers, more significantly in the liver than in the brain. These findings support the thesis that there may be a relationship between oxidative and endoplasmic reticulum stress, as mentioned in the literature [12,24,39].

The endoplasmic reticulum is an important organelle in all eukaryotic cells that is responsible for the correct folding of proteins after transcription and reaching their target site [50]. Excessive accumulation of unfolded or misfolded proteins in the endoplasmic reticulum lumen causes endoplasmic reticulum stress. To correct this situation, a complex mechanism called UPR is initiated. The UPR mechanism is a homeostatic response to repair the disturbed balance between folded protein production and unfolded protein production. PERK, ATF6, and GRP78 proteins play an important role in the UPR mechanism [12-14].

Hengjiang, et al. determined that PERK, ATF6, and GRP78 levels in the kidney tissues of diabetic mice were statistically significantly higher than in the control group. In the same study, they showed that PERK, ATF6, and GRP78 levels in mice with astragaloside IV were statistically significantly lower than in diabetic mice. They also showed that the levels of caspase 3, caspase 9, and caspase 12, which are effective on the apoptotic pathway, were statistically significantly higher in mice in the diabetic group compared to those in the control group, and the levels of the same molecules in the antioxidant group were statistically significantly lower than in the diabetic group [51]. Another study conducted by Feng et al. showed that PERK, GRP78, and CHOP levels in the brain hippocampus tissues of diabetic rats were statistically significantly higher than in the control group; however, administration of vitamin D as an antioxidant statistically lowers these UPR markers [33]. There were also some studies to underscore that the increased levels of p-PERK, CHOP, and ATF6 in different tissues of diabetic rats, and the administration of variable antioxidants lowers the levels of these markers [52,53].

In our study, ATF6 and GRP78 levels in the brain tissues of rats in the diabetic group were found to be statistically significantly higher than those in the control group. The PERK levels of the diabetic group were found to be higher than those of the control group, although it was not statistically significant. The PERK, ATF6, and GRP78 levels of the rats in diabetic antioxidant group were found to be statistically significantly lower compared to the diabetic counterpart. Our results are parallel with the aforementioned literature.

Consequently, we evaluated the PERK and GRP78 levels of the liver tissues. These UPR markers increased in the

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diabetic group as compared to the control group, however, the antioxidant molecule Q10 administration to the diabetic antioxidant group decreased the levels of PERK and GRP78 as compared to the diabetic group.

The UPR mechanism against endoplasmic reticulum stress is responsible for restoring homeostasis in the cell [1]. In cases where the UPR is not sufficient, the endoplasmic reticulum-mediated signal cascade in the cell is initiated and apoptosis is triggered. Cell death leads to loss of tissue function and may be the cause of various diseases related to endoplasmic reticulum stress. Apoptosis is thought to be the most important cause of pancreatic beta-cell loss, especially in type I diabetes patients [12,13,54].

TWEAK, which is claimed to have a proapoptotic effect, binds to its receptor called Fn14 under various pathological conditions and stimulates many mechanisms [55,56]. Studies show that TWEAK/Fn14 receptor binding in the brain causes neuronal apoptosis in the pathogenesis of stroke and also contributes to an increase in the permeability of the blood-brain barrier in cerebral ischemia. In addition, the findings in these studies that show increased TWEAK and Fn14 expressions in the ischemic brain of stroke patients and in animal models of cerebral ischemia also support this opinion [57,58]. The TWEAK/Fn14 interaction during cerebral ischemia activates the transcription factor NF-kβ pathway. This interaction also induces the expression of MMP-9, proinflammatory cytokines and chemokines, recruitment of neutrophils, disruption of the blood-brain barrier, and neurodegeneration. In light of these studies, a hypothesis has been proposed that claims TWEAK-Fn14 antagonists may limit brain damage [59,60].

In our study, we aimed to reduce TWEAK-Fn14 binding in the brain tissues of diabetic rats with the coenzyme Q10 antioxidant. The findings revealed that the TWEAK levels of the diabetic antioxidant group were statistically significantly lower than those of the diabetic group. Although there are some studies suggesting a relationship between TWEAK and endoplasmic reticulum stress, none explains the whole mechanism in question (19). In our study, we examined the possible relationship between the TWEAK molecule with UPR signaling pathways which might explain their possible role in endoplasmic reticulum stress. Our results showed a statistically significant positive correlation between TWEAK and UPR proteins (ATF6, GRP78). We also observed a positive relationship between TWEAK and PERK. These findings may link the TWEAK molecule to endoplasmic reticulum stress by the UPR mechanism.

In the liver tissue there was a decline in the level of TWEAK molecules as compared to the control group. Tiller et al. claimed that there was no TWEAK receptor on adipocytes and mature liver cells, and therefore TWEAK could not affect these cells [61]. This claim supports our findings.

In consideration of the aforementioned factors, it can be concluded that the use of coenzyme Q10 for a certain period has a glucose-lowering effect. Coenzyme Q10 reduces oxidative stress and endoplasmic reticulum stress (especially in brain tissue) and increases antioxidant levels. Consequently, these findings suggest that coenzyme Q10 has a positive effect on reducing diabetic brain damage. In our study, the correlation between oxidative stress parameters and endoplasmic reticulum parameters supports the positive relationship between them. The relationship between TWEAK and endoplasmic reticulum stress has not been fully illuminated, but the finding of a positive correlation in our study may lead to a new way of addressing this issue.

Acknowledgments

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