Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;10(2):391-5

Increased levels of thioredoxin and thioredoxin reductase in diabetic patients with coronary artery disease

Necat Yilmaz, Cihan Demir, Esin Eren

Antalya Egitim ve Arastirma Hastanesi, LCMS-MS Laboratory, Antalya, Turkey

Received 18 September 2020; Accepted 25 November 2020
Available online 25.03.2021 with doi: 10.5455/medscience.2020.09.189

Abstract

The prevalence of type 2 diabetes (DM) is considered an important risk factor for coronary artery disease (CAD). This study aimed to evaluate the relationship between CAD and thioredoxin (Trx) system and novel lipid indices in DM patients. In this case-control study, serum levels of Trx, Thioredoxin reductase (TrxR), Thioredoxin interacting protein (TXNIP), and novel lipid indices in DM undergoing coronary angiography (CAG) was investigated. A total of 99 patients with DM were included in the study (DM + CAD n: 62 and DM n: 37. Serum levels of intracellular antioxidant defense molecules, Trx and TrxR were significantly increased in patients with CAD+DM. However, TXNIP serum levels did not differ significantly between DM+CAD and DM groups. Also, there was a significant positive correlation between Trx and TXNIP ($p < 0.001$). The most important finding of this first study, which examined the thioredoxin system in the literature, is that it shows that the Trx system in diabetes-affected CAD may have mediated a possible compensatory mechanism due to glucotoxicity in DM.

Keywords: Coronary artery disease, thioredoxin interacting protein, thioredoxin, oxidative stress, diabetes mellitus

Introduction

In nowadays, the diabetic disease state with hyperglycemic conditions has been associated with an increase in oxidative stress (OS). Already, OS may be classified as a "chemical silent killer" [1, 2]. Primary antioxidants are those that directly react with free radicals yielding less reactive species or finishing the radical chain reaction. Secondary antioxidants exert their protection by mechanisms that do not involve direct reactions with free radicals such as antioxidant enzymes [2, 3]. Trx has two forms: oxidized Trx-S2 and reduced Trx-(SH)2. The reduced Trx may be transformed into oxidized Trx in the process of scavenging free radicals. Fortunately, under the action of the TxrR enzyme, the oxidized Trx may take electrons from NADPH and return to reduced Trx [4,5]. Therefore, Trx could play important roles in the development of CAD either through its ability to attenuate the level of OS or through alterations in redox-sensitive signaling, which has diverse effects on CAD pathophysiology [6-8]. In short, the mammalian selenoprotein TrxR enzyme encoded by the TXNRD1 gene in humans plays a key role in antioxidant defense, redox regulation, cell proliferation, and cell signaling by catalyzing the reduction of Trx's active site disulfide in cells [9,10].

As thiol-disulfide exchange reactions are fast and easily reversible, these intracellular reactions are ideally suited for controlling protein function through the redox state of structural or catalytic SH groups. Intracellular reactions that can be controlled, for example, defense against OS includes gene transcription, cell growth, cell survival and death, and protein quality control [7-10]. Consequently, the study of diabetic patients revealed a significant increase in serum Trx / TrxR levels naturally compared to normoglycemic controls [11,12]. Of course, an upper regulation of the Trx / TrxR system is assumed to act protectively against the complications of DM. Because ultimately because Trx is an antioxidant enzyme, it causes an increase in Trx against OS due to hyperglycemia. The Trx / TrxR system, which is a redox control system, can also regulate the inflammatory and chemotactic activity of macrophages at different stages of atherosclerotic plaque formation [13-15].

***Corresponding Author:** Necat Yilmaz, Antalya Egitim ve Arastirma Hastanesi, LCMS-MS Laboratory, Antalya, Turkey. E-mail: necatyilmaz@hotmail.com

Conversely, TXNIP binds to and inhibits intracellular Trx and thus can modulate the cellular redox state and induce OS. TXNIP is a physiological, internal Trx regulatory protein that can bind with Trx, and bound Trx loses inhibition of cell apoptosis, thus increasing cell apoptosis [14-16]. Higher serum TXNIP levels in impaired glucose tolerance are indicative of the potential of TXNIP measurement as a tool for atherosclerosis prediction in diabetic patients [16]. The Trx / TXNIP ratio referred to as "redoxisome", may indicate intracellular antioxidant balance and may be involved in the pathogenesis of various diseases such as cancer, autoimmune disease, and diabetes [15].

Yet, there is no study in the literature showing the contribution of redoxisome to CAD development in DM patients. Also, it is not known whether there is a relationship between the Trx system and diabetic CAD. Therefore, a detailed understanding of the Trx, TrxR, and TXNIP changes in DM+CAD patients may be important to understand the heart complications of DM. This study aimed to evaluate the association of the Trx system markers with CAD in DM patients.

Material and Methods

Subjects

Demographic and clinical data of 117 types 2 DM participants who underwent elective CAG were evaluated. This cross-sectional study was observational because no intervention was attempted, and no attempt was made to alter the course of the disease. In calculating the number of samples in this study online calculator program was used. Sample population was unlimited population size and DM prevalence was 10% in this program (formula for sample size: SS=Z2p(1−p)/C2 and calculated sample size: 139) (16). A research sample was created with 99 male types 2 diabetes participants who met the inclusion criteria and had no exclusion criteria. All the participants were divided into two groups according to the DM+CAD and only DM. The study group consisted of 62 patients with DM+CAD, and 37 DM patients (table 1). Inform consent forms were obtained from all patients participating in the study. This work was carried out following the ethical standards set forth by the Declaration of Helsinki (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf) and was approved by the local ethics committee decision numbered 76/21. Age and gender data of the subjects were recorded; anthropometric measurements (height and body weight) were performed and body mass index (BMI) (kg/m^2) was calculated. The history of cardiac disease (CAD, congestive heart failure, and arrhythmias) and history of non-cardiac chronic disease (bronchial asthma, chronic obstructive pulmonary disease, thyroid dysfunction, and thalassemia) were questioned. Major inclusion, criteria were adult patients (≥18 years of age) with suspected CAD. The main exclusion criteria were a history of type 1 DM and other exclusions criteria; patients with known CAD, patients who have had previous revascularization (CABG, PTCA, stenting). Also, some subjects were excluded for having chronic diseases and used drugs (e.g., lipid-lowering drugs / antioxidant drugs). Informed consent (Informed Volunteerism and Consent Form) was given to the patient group and the control group.

Samples

Blood samples from the participants were taken to tubes with vacuum separator gel after 12 hours of night fasting. Serum samples obtained after centrifugation of blood samples were stored at -80°C.

Routine biochemical tests

Autoanalyzer Beckman AU5800® (Beckman Coulter Diagnostics, CA, USA) for the measurement of glucose, creatinine, gamma-glutamyl transpeptidase, uric acid, and lipid panel (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides) used in the study and commercial diagnostic reagent kits of the same brand were used. HbA1c analyzes of the participants were performed by using the method, Tosoh high-pressure liquid chromatography -723® G7 glyco-hemoglobin autoanalyzer.

In the study, the Unicel DXI 800 immunoassay system for insulin, parathormone, ferritin, vitamin B12 (Beckman Coulter diagnose, CA, USA) was used in the same brand access DXI 800 automated diagnostic and commercial reagent kits (Beckman Coulter Inc., CA, USA). Diagnostic reagent kits were used for the measurement of 25-Hydroxy Vitamin D in auto-analyzer Liaison® (DiaSorin SpA, Saluggia, VC, Italy).

Table 1. The clinical characteristics of the diabetes mellitus patients with coronary artery disease and diabetes mellitus patients with normal coronary arteries.

Parameter	CAD + DM (n=62)	No-CAD + DM (n=37)	p value
Age (year)*	60.6 ± 9.2	56.5 ± 8.1	0.041
Male gender, n (%)	38 (61.2)	10 (37.0)	0.12
Body weight (kg)**	80 (70-88)	77 (65-86)	0.45
BMI (kg/m^2)*	28.1 ± 3.5	27.8 ± 3.2	0.71
Herbal medication, n (%)	18 (29.0)	4 (14.8)	0.15
Hypertension, n (%)	44 (70.9)	15 (55.5)	0.16
Early cardiac event in family, n (%)	22 (35.4)	12 (44.4)	0.42
Smoking, n (%)	35 (56.4)	14 (51.8)	0.69
AF presence on ECG, n (%)	7 (11.2)	1 (3.7)	0.25
Ischemic findings on ECG, n (%)	9 (14.5)	1 (3.7)	0.14
Severe valvular disease presence, n (%)	8 (12.9)	3 (11.1)	0.81
LVEF (%)**	60 (45-65)	65 (60-65)	<0.001

Pearson Chi-Square test for frequencies, *Mean±SD / t-test for independent samples, **Median (IQR) / Mann-Whitney U test, BMI: Body Mass Index, AF: Atrial fibrillation, ECG: Electrocardiogram, LVEF: Left ventricular ejection fraction

Table 2. Laboratory findings of diabetes mellitus +coronary artery disease patients and diabetes mellitus patients.

Parameters Mean± S.E.M. or IQR	DM + CAD (n= 62)	Non-CAD + DM (n=37)	p value
Trx (ng/mL)	76.03 (63 - 88)	56.61 (48.80 - 65.60)	0.013**
TrxR (ng/mL)	1.60 (0.94 – 2.26)	0.88 (0.56 - 1.20)	<0.001**
TXNIP (pg/mL)	54.80 (32.96 -76.72)	40.7 (18 - 62)	0.064
Trx/TXNIP	1.38	1.39	0.83
Glukoz (mg/dL)	134.0 (118.60-150.20)	115.7 (107-157)	0.062
Non HDL-C	3.72 ± 1.32	3.61 ± 1.14	0.046*
HbA1C (%)	6.9 (6.30 – 7.50)	6.8 (5.80 -7.60)	0. 59
Insulin (µIU/mL)	24.75 (13.24- 29.37)	22.06 (10 - 34)	0.12
HOMA-IR	11.65 (7.70 -14.90)	11.35 (6.03 -17.2)	0.46
Uric acid (mg/dL)	5.5 (3.80 - 4.90)	4.70 (4.90 – 5.90)	0.012**
Creatinine (mg/dL)	1.04 (0.98 -1.10)	0.92 (0.85 – 0.99)	0.12
PTH (pg/mL)	38.30 (34.50 – 2.90)	38.70 (33.00 – 44.50)	0.27
25-OH vitamin-D3 (ng/mL)	14.60 (12.90 – 26.20)	12.0 (9.10 – 21.20)	0.73
Vitamin B12 (pg/mL)	210 (194 – 332)	177 (168 – 249)	0.084
Ferritin (ng/mL)	47.90 (40.10 – 81.70)	60 (37.30 – 82.70)	0.063
Total Cholesterol (mg/dL)	192 (175 - 209)	204 (184 - 223)	0.69
Triglycerides (mg/dL)	169 (126 - 184)	145 (134 - 217)	0.34
HDL Cholesterol (mg/dL)	44.50 ± 1.64	48.60 ± 1.83	0.21
LDL Cholesterol (mg/dL)	136.90 ± 7.01	125.40 ± 6.83	0.26

*Unpaired t test, **Mann-Whitney U test, Trx:thioredoxin, TrxR:thioredoxin, reductase, TXNIP:thioredoxin interacting protein, HbA1C:Hemoglobin A1c, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance, PTH: Parathormone,25-OH vitamin-D3:vitamin D

Thioredoxin

Serum Trx analyzes of the participants was performed using the quantitative Enzyme-Linked Immunosorbent Assay (ELISA) immunoassay method using Human Trx study kit (Catalog No: CSB-E09728h, Cusabio Biotech Corporation, Wuhan, Hubei, China). The analytical linearity of the test reagent used was determined as 4.688-300 ng/mL for serum Trx concentration. The highest in-study variation coefficient (CV) was lower than 8% and the highest in-study CV was lower than 10%.

Thioredoxin reductase

Serum TrxR enzyme analyzes of the participants was performed using a quantitative ELISA method using the Human TrxR study kit (Catalog No: CSB-E09731h, Cusabio Biotech Corporation, Wuhan, Hubei, China). The analytical linearity of the test reagent used was determined as 0.312-20 ng/mL for serum TrxR concentration. The highest in-study variation coefficient (CV) was lower than 8% and the highest in-study CV was lower than 10%.

Thioredoxin interacting protein

Serum TXNIP analyzes of the participants were performed using a quantitative ELISA method using the Human TXNIP study kit (Catalog No: CSB-EL025383HU, Cusabio Biotech Corporation, Wuhan, Hubei, China). The analytical linearity of the test reagent used was determined as 15.6 - 1.000 pg/mL for the serum TXNIP concentration. The highest in-study variation coefficient (CV) was lower than 8% and the highest in-study CV was lower than 10%.

Statistical analysis

Descriptive statistics were used for the results of categorical variables such as smoking, number, and frequency. Continuous variables were expressed as mean ±standard error of the mean (S.E.M). The statistical analysis was performed using MedCalc© Statistical Software version 15, 8 (MedCalc Software® bvba, Ostend, Belgium; https://www.medcalc.org; 2018). The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. For comparison of variables with a normal distribution unpaired, 2-tailed Student's t-test and Pearson's correlation were used, whereas the Mann–Whitney U-test was used for variables with a skewed distribution to analyze clinical and laboratory data. Categorical data were presented as number and percentage (%) and compared by chi-square test. DeLong methodology was used to compare measurements receiver operator characteristics curve (ROC) and area under the curve (AUC). A $p \leq 0.05$ was considered statistically significant.

Results

The study included 62 male patients with DM + CAD with a mean age of 60.6 ± 9.2 years and 37 non-CAD DM male patients with a mean age of 56.5 ± 8.1 years (p=0.041). Comparison of clinical and demographic data of all two groups is shown in table 1. In terms of clinical findings, the present rates of chronic arrhythmias and ischemia findings were similar in two groups, p=0.763. When the values of left ventricular ejection fraction (LVEF) percentages were compared, a significant difference was found between the groups (p <0.001, table 1).

There is no statistically significant difference between the two groups between the levels of other risk factors (25-Hydroxy vitamin, vitamin B12, insulin, parathormone, ferritin), which may play an important role in CAD development.

Serum Trx values of DM + CAD patients were statistically significantly higher than those with DM patients. The median concentration of Trx was 76.03 ng/mL in DM + CAD group, and 56.61 ng/mL in control group (table 2, p=0.013). Also, the median concentration of serum TrxR enzyme was 1.6 ng/mL in the DM + CAD group and 0.88 ng/mL in the control group. There was a significant difference between these groups in terms of TrxR enzyme concentrations (p< 0.001, table 2). TXNIP concentration was higher in DM + CAD group than in the control group. However no statistically significant difference was found between the groups in terms of TXNIP concentrations (p=0.064, table 2, figure 3). However, we did not find a statistically significant difference in TRX / TXNIP ratios between both groups (Table 2).

Also, a positive correlation was found between TXNIP and TrxR (r=0.393, p=0.0045). In addition, there were a strong positive correlation between Trx and TrxR (r = 0.508, p <0.0001) and positive correlation between TrxR and HbA1c (r = 0.25, p =0.038). Unfortunately, the diagnostic values of Trx TrxR and TXNIP for excellent biomarker were not high. The receiver operating characteristic curve (ROC) of the intracellular antioxidant markers (Trx system) were shown in Figure 1. The AUC-Trx: 0.61, AUC-TrxR: 0.56, and as low as AUC-TXNIP: 0.56, finally our results showed that these tests have low sensitivity and specificity for diabetic CAD (figure 1).

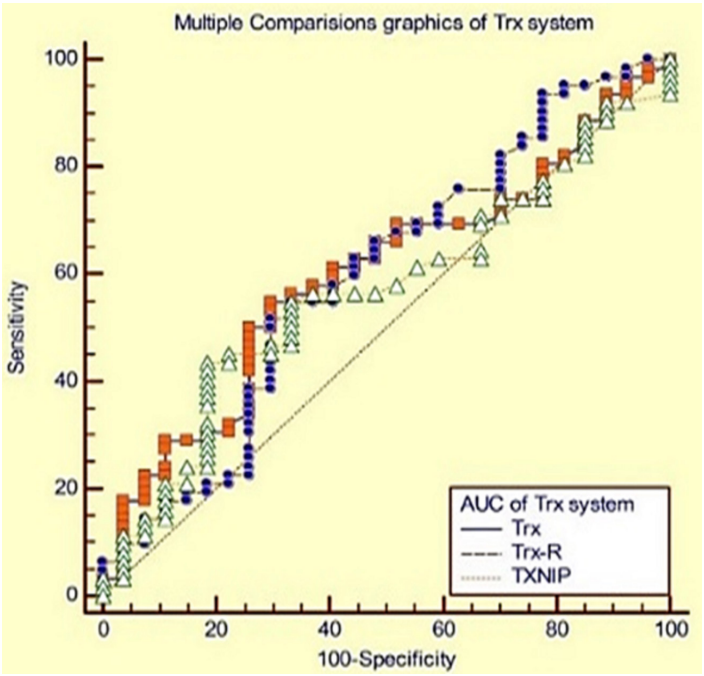

Figure 1: A receiver operator characteristics curve of the thioredoxin system in DM patients. In a Receiver Operating Characteristic (ROC) curve the true positive rate (Sensitivity) was plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/ specificity pair corresponding to a particular decision threshold.

Discussion

The main finding of this study is that DM patients encourage the intracellular antioxidant defense system against CAD. So, Trx and TrxR serum levels were higher in DM+CAD patients than DM patients. In patients with DM+CAD, increased Trx and TrxR may eventually be a compensatory response against oxidative damage associated with DM. So, an upregulation of the strong intracellular antioxidative Trx/TrxR system is presumed to act protectively against further complications of diabetes. Of course, modulation of the Trx/TrxR system in DM is may be considered as a compensatory response to diabetes-related OS, aiming at the prevention of further metabolic complications [17- 20]. For instance, previously had reported that exposure of human macrophages to oxidized LDL (ox-LDL) was associated with stimulation of Trx and TrxR expression (6, 20). So, modulation of the Trx/TrxR in serum may play a significant role at the initial stages of atherogenesis and its progression [8, 21]. In particular, atorvastatin treatment of endothelial cells resulted in an accompanying increase in Trx activity and a significant reduction in reactive oxygen species (ROS) levels [22, 23]. As expected, drugs of the Trx system appears a success in pre-clinical trials [24-26]. For instance, the use of Trx mimetic peptide; CB3 was of great importance in a study that might reduce inflammation and atherosclerotic lesions in atherosclerotic patients [22, 23].

As expected in our study, higher TXNIP levels were found in DM + CAD patients, consistent with induced expression with hyperglycemia. However, the difference was not statistically significant compared to the DM patients and the DM + CAD patients. The positive correlation between Trx and TrxR and TXNIP and TrxR found in the correlation analysis of the diabetic CAD patients reflects the increasing trend of the antioxidative mechanisms in the pathogenesis of hyperglycemia. At the same time, the positive correlation of TrxR with HbA1c was significant in terms of showing the increased activity of antioxidant systems to compensate for increased OS in DM pathogenesis. The previous study has revealed the potential protective effect of the Trx/TrxR (peroxisome)system against progressive pancreatic β-cell damage (26). As a result, the Trx system may have protective potential effects on diabetic CAD [15,16]. However, the increase of TXNIP may result in inhibition of the Trx system in diabetes [14,26]. In some previously reported articles, it has been reported that very high glucose levels significantly reduce Trx activity by up-regulation of TXNIP expression through the p38 mitogen-activated protein kinase signaling pathway. However, patients in our study group did not have very high glucose levels. Therefore, the increase in TXNIP was may limited. Therefore, both the peroxisome system and its antagonistic principle TXNIP have been proposed as potential targets for anti-diabetic and cardiovascular therapy [13, 15, 27].

One of the major limitations in our study is the inability to measure intracellular redox balance. Of course, serum measurement of the Trx system, which is part of the intracellular antioxidant system, Trx can yield limited information. Also, the most important limitation of this study is the small number of subjects and low statistical power. Identification of specific abnormalities in the Trx system and strategies for correcting them may lead to innovative approaches that favorably modify various forms of CAD including coronary heart disease and many other pathological states. The present preliminary study shows that the Trx/TrxR system might play a significant role in the body defense against DM related OS.

The results of this study may suggest that the high glucose levels occurring in DM increased Trx and TrxR levels to compensate for increased ROS production and OS, which may increase intracellular [26].

Conclusion

We think that intracellular antioxidant peroxisome balance may play a role in the development of CAD in diabetic patients, it is undoubtedly a preliminary study and if supported by larger clinical studies in the future, the thioredoxin system can be used as a target to prevent diabetic complications and to develop drugs

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Antalya Training and Research Hospital ethics committee protocol numbered 76/21.

References

1. Wang DS, Yan LY, Yang DZ, et al. Formononetin ameliorates myocardial ischemia/reperfusion injury in rats by suppressing the ROS-TXNIP-NLRP3 pathway. Biochem Biophys Res Commun. 2020; 4: pii: S0006-291X (20)30436-8.
2. Rong J, Xu X, Xiang Y, et al. Thioredoxin-interacting protein promotes activation and inflammation of monocytes with DNA demethylation in coronary artery disease. J Cell Mol Med. 2020;24:3560-3571.
3. Poljsak B, Milisav I. The neglected significance of "antioxidative stress". Oxid Med Cell Longev. 2012;2012:480895.
4. Zschauer TC, Matsushima S, Altschmied J, et al. Interacting with thioredoxin-1-disease or no disease? Antioxid Redox Signal. 2013;20:18:1053-62.
5. Lee S, Kim SM, Lee RT. Thioredoxin and thioredoxin target proteins: from molecular mechanisms to functional significance. Antioxid Redox Signal. 2013;1;18:1165-207.
6. Oliveira PVS, Laurindo FRM. Implications of plasma thiol redox in disease. Clin Sci (Lond). 2018;21;132:1257-80.
7. Mahmood DF, Abderrazak A, El Hadri K, et al. The thioredoxin system as a therapeutic target in human health and disease. Antioxid Redox Signal. 2013;10;19:1266-303.
8. Ren X, Zou L, Lu J, Holmgren A. Selenocysteine in mammalian thioredoxin reductase and application of ebselen as a therapeutic. Free Radic Biol Med. 2018;1;127:238-47.
9. Miller CG, Holmgren A, Arnér ESJ, et al. NADPH-dependent and -independent disulfide reductase systems. Free Radic Biol Med. 20181;127:248-61.
10. Gu C, Liu S, Wang H, Dou H. Role of the thioredoxin interacting protein in diabetic nephropathy and the mechanism of regulating NOD-like receptor protein 3 inflammatory corpuscle. Int J Mol Med. 2019;43:2440-50.
11. Kariž S, Mankoč S, Petrovič D. Association of thioredoxin reductase 2 (TXNRD2) gene polymorphisms with myocardial infarction in Slovene patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2015;108:323-8.
12. Zhao X, Zhang Y, Li X, et al. Variations of thioredoxin system contributes to increased susceptibility to apoptosis in cardiomyocytes of type 2 diabetic rats. Acta Biochim Biophys Sin (Shanghai). 2014;46:318-29.
13. El Hadri K, Mahmood DF, Couchie D, et al. Thioredoxin-1 promotes anti-inflammatory macrophages of the M2 phenotype and antagonizes atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32:1445-52.
14. Yoshihara E, Masaki S, Matsuo Y, et al. Thioredoxin/Txnip: redoxisome, as a redox switch for the pathogenesis of diseases. Front Immunol. 2014;9;4-514.
15. Whayne TF Jr, Parinandi N, Maulik N. Thioredoxins in cardiovascular disease. Can J Physiol Pharmacol. 2015;93:903-11.
16. Kamangar F, Islami F.Sample size calculation for epidemiologic studies: principles and methods. Arch Iran Med. 2013;16:295-300.
17. El Hadri K, Mahmood DF, Couchie D, et.al. Thioredoxin-1 promotes anti-inflammatory macrophages of the M2 phenotype and antagonizes atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32:1445-52.
18. Chen B, Meng L, Shen T, et al. Thioredoxin attenuates oxidized low-density lipoprotein induced oxidative stress in human umbilical vein endothelial cells by reducing NADPH oxidase activity. Biochem Biophys Res Commun. 2017;2;490:1326-33.
19. Cao G, Llambí HG, Muller A, et al. Rosuvastatin increases myocardial microvessels in SHR rats. Role of thioredoxin-1 and peroxiredoxin-2 expression. Int J Cardiol. 2014;1;174:153-5.
20. Lu J, Holmgren A. The thioredoxin antioxidant system. Free Radic Biol Med. 2014;66:75-87.
21. Harper MT. Auranofin, a thioredoxin reductase inhibitor, causes platelet death through calcium overload. Platelets. 2019;30:98-104.
22. Roder C, Thomson MJ. Auranofin: repurposing an old drug for a golden new age. Drugs R D. 2015;15:13-20.
23. Canesi F, Mateo V, Couchie D, et al. Thioredoxin-mimetic peptide exerts potent anti-inflammatory, anti-oxidant and atheroprotective effects in ApoE2. Ki mice fed high fat diet. Cardiovasc Res. 2019;1;115:292-301.
24. Cohen-Kutner M, Khomsky L, Trus M, Thioredoxin-mimetic peptide CB3 lowers MAPKinase activity in the Zucker rat brain. Redox Biol. 2014;9;2:447-56.
25. Yilmaz N. Relationship between paraoxonase and homocysteine: crossroads of oxidative diseases. Arch Med Sci. 2012;29;8:138-53.
26. Tinkov AA, Bjørklund G, Skalny AV, et al. The role of the thioredoxin/thioredoxin reductase system in the metabolic syndrome: towards a possible prognostic marker? Cell Mol Life Sci. 2018; 75:1567-86.
27. Hou R, Shen M, Wang R, et al. Thioredoxin1 Inactivation Mediates the Impairment of Ischemia-Induced Angiogenesis and Further Injury in Diabetic Myocardium Vasc Res. 2020;57:76-85.