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REVIEW ARTICLE

Clinical Utility of Thiol/Disulfide Homeostasis

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SUMMARY

Background: **Recently, the usefulness of thiol/disulfide homeostasis (TDH) in various diseases is being widely investigated. In this mini-review, our aim is to clarify the role of TDH in clinical practice in the light of current literature.**
Methods: **We performed a systematic review of the existing literature describing the clinical utility of TDH in the clinical setting. MEDLINE, EMBASE, and CINAHL were used as data sources. Two reviewers conducted independent screening and data extraction. Use of TDH in each system was investigated separately.**
Results: **A total of 35 studies were detected in this mini-review. Our results revealed the protective role of TDH and its utility as a diagnostic marker in many common diseases in clinical practice.**
Conclusions: **Maintenance of TDH as a crucial part of antioxidant defense system is critical in diagnosis and prognosis of potentially lethal diseases.**
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INTRODUCTION

Thiols are important antioxidant agents in human beings. Thiols are available as free or oxidized forms in plasma. The thiol pool of plasma is mainly composed of protein thiols including albumin and, to a lesser extent, low molecular mass thiols [1]. In case of high oxidative stress, thiol levels decrease in order to neutralize the reactive oxygen species. In this case, sulfhydryl groups of thiols play a critical role [2]. Upon oxidative stress, disulfide bonds undergo reversible formation between protein and low molecular weight thiols. These bonds may be reduced back to thiols, and thus thiol/disulfide homeostasis is sustained [3,4]. Thiols contain a sulfhydryl group (-SH), which is composed of a hydrogen and a sulfur atom attached to a carbon atom. The plasma thiol pool is largely formed by albumin and protein thiols and, to a lesser extent, by low-molecular weight thiols such as cysteinylglycine, cysteine, homocysteine, glutathione, and g-glutamylcysteine [1]. Oxidative stress occurs due to an imbalance between antioxidants

and reactive oxygen species (ROS). In high oxidative stress, thiol concentrations decline to neutralize ROS. Thiols can undergo oxidation reaction via oxidants and form disulphide bonds, which can be reduced back to thiol groups; therefore, thiol-disulphide homeostasis is maintained [4]. Thus, TDH plays an important role in the antioxidant defense system [5].

Detection of thiol/disulfide homeostasis

Since thiols are highly reactive, they can be detected directly; however, disulfides can be detected after reduction to their corresponding thiols. Thus, the most common methodologies for thiol and disulfide detection involve determination of free thiol concentration, followed by alkylation, reduction of disulfide bonds by phosphine- and thiol-based reductants, and subsequent quantification of the additional exposed thiols. On the other hand, thiols can be detected via colorimetric methods, fluorescent adducts, and formation of detectable thiol adducts using gel-shift assays [6].

Cardiac diseases and thiol/disulfide homeostasis

Irreversible oxidative modifications due to oxidation/reduction of protein thiols are known to play a role in the pathogenesis of cardiovascular diseases [7].

Altiparmak et al. sought for possible alterations of TDH in relation to the severity of coronary artery diseases. In their study, they compared serum thiol levels in patients with critical and non-critical coronary artery stenosis. They revealed that thiol levels were significantly lower in patients with critical stenosis. However, when disulfide/thiol ratio was calculated, it was revealed that the ratio increased minimally with the severity of the disease. This finding was not statistically significant. They also calculated the Gensini scores, which is a method used to determine the degree of luminal narrowing and distribution, and they determined significant negative correlations between Gensini scores and native thiol, total thiol, and disulfide levels [3]. On the other hand, Kundi et al. investigated TDH in both patients with acute myocardial infarction (AMI) and healthy controls. They determined significant differences in left ventricular ejection fraction and troponin, HDL, native thiol, total thiol, and disulphide levels as well as disulphide/native thiol and disulphide/total thiol ratios between AMI patients and the controls. As a conclusion, they proposed TDH as a novel marker in diagnosis of AMI [8].

In another study, Altiparmak et al. investigated serum TDH levels in Cardiac Syndrome X - a syndrome characterized by the presence of myocardial ischemia without coronary artery stenosis on angiograms. They reported increased levels of TDH in patients with syndrome; however, this finding was not significant [9]. It was also reported by Kiziltunc et al. that TDH levels in patients with coronary artery ectasia was higher than that of healthy controls. Their results also revealed that thiol/disulfide ratio was not different according to the number of the ectatic coronary arteries and there was no association between thiol/disulfide ratio and the classification system established by Markis et al. in 1976 in order to determine the extension of ectasia [10-12].

Neurological diseases and thiol/disulfide homeostasis

In 1995, Shiwakumar et al. determined rapid restoration of thiol homeostasis in the brain during reperfusion after cerebral ischemia in rats. Their report underlined the potential protective role of thiol homeostasis from reperfusion injury [13].

Bektas et al. investigated TDH in patients with acute ischemic stroke confirmed by magnetic resonance diffusion-weighted imaging within the first 24 hours. They measured thiol, disulfide, and total thiol levels in the 24th and 72nd hours and compared the findings with international stroke scales. In patients with moderate and severe stroke, thiol levels were significantly lower than in patients with mild stroke [14].

Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disorder caused by a trinucleotide CAG repeat expansion in exon-1 of the Huntingtin gene [15]. In a study with mice, they determined that thioredoxin 1 (TRX1) and thioredoxin-related transmembrane protein 3 (TMX3) as the proteins that decrease both mHTT levels in cultured cells and mHTT-induced striatal neuronal atrophy in HD mice, which might indicate the role of TDH in the pathogenesis of HD [16].

Carbon monoxide (CO) causes tissue damage by asphyxia and cellular hypoxia via binding to hemoglobin, myoglobin, and cytochrome p450 and by ischemia and reperfusion injury [17]. Since the central nervous system has high sensitivity to poisoning, it may cause symptoms varying from headache to coma [18,19]. In a study by Ergin et al., an alteration in the thiol-disulfide balance was determined in CO-poisoned patients. They also concluded that the disruption of TDH might be involved in CO toxicity, further investigations are needed in this field [20].

Additionally, in patients with sudden sensorineural hearing loss, lower native thiol levels than controls were determined which might have been evidence for the relationship between sudden sensorineural hearing loss and oxidative stress [21].

Gynecologic diseases and thiol/disulfide homeostasis

Erkenekli et al. investigated TDH in 39 pregnant women diagnosed with idiopathic recurrent pregnancy loss (RPL) and compared with 50 healthy pregnant women without a history of abortion. They found that patients with idiopathic RPL had significantly lower plasma levels of native thiol and total thiol. Disulfide/thiol and disulfide/total thiol ratios were significantly higher in the study group. They also reported that native thiol/total thiol ratio was significantly lower in patients with idiopathic RPL [22].

In another study, it was reported that disulfide levels, disulfide/native thiol and disulfide/totalthiol ratios were significantly increased, and native thiol/total thiol levels were significantly decreased in premature ovarian fail-

ure patients compared to controls [23].
When pregnant women with no obstetric complications, pregnant women with mild preeclampsia, and pregnant women with severe preeclampsia were compared according to TDH levels, Korkmaz et al. stated in their report, that TDH levels tended to significantly decrease as the disease worsens. Alterations in levels of TDH might play an important role in the pathogenesis of TDH [24].
In patients with hyperemesis gravidarum, native and total thiol were found to be deficient, and this deficiency was correlated with the severity of the disease [25].
When TDH levels in women with neural tube defect (NTD) were investigated, it was reported that TDH levels were not affected in pregnancies complicated by NTD [26]. When the effect of maternal obesity and gestational diabetes mellitus (GDM) on cord blood dynamicthiol/disulfide homeostasis was investigated, it was reported that disulfide amounts, disulfide/native thiol, and disulfide/total thiol ratios increased, while native thiol/ total thiol decreased in the cord blood of babies born to an obese or diabetic mother. It was also reported that increased disulfide amounts, disulfide/native thiol, disulfide/total thiol ratios, and decreased native/total thiol were found to be significantly associated with adverse outcomes in GDM. Newborns of obese or diabetic mothers are thought to be at risk to stress related oxidants [27].

Pulmonary diseases and thiol/disulfide homeostasis
Topuz et al. investigated the relationship between TDH and pulmonary embolus (PE). They divided patients with acute PE into subgroups according to severity. They have determined alterations in TDH levels and proposed TDH as a prognostic marker in patients with PE [28]. Babaoğlu et al. investigated TDH levels in patients with chronic obstructive pulmonary disease (COPD), asthma and asthma-COPD overlap syndrome (ACOS). Serum values of these parameters in these diseases were similar. They concluded that this finding supported that COPD, asthma and ACOS share similar pathophysiological features but display different clinical manifestations [29].

Blood disorders and thiol/disulfide homeostasis
In a study with patients with multiple myeloma, while native and total thiol levels in the control group were determined to be higher than in the study and patient groups, disulfide levels were found to be higher in the control group than in the study group. It was also determined that newly diagnosed patients had higher disulfide values than outpatients who were undergoing treatment. It was reported that the balance was protected [30].
Hematological changes in Crimean-Congo Hemorrhagic Fever (CCHF) are well-described in the literature [31, 32]. When oxidant-antioxidant balance in patients with CCHF was detected, it was reported that TDH shifts to the oxidative side in patients with CCHF, leading to an increase in total oxidant status (TOS). They determined that while disulfide/native thiol and disulfide/total thiol ratios and TOS increased, total antioxidant status decreased in patients with CCHF [33].

Endocrine diseases and thiol/disulfide homeostasis
Ateş et al. have shown that thiol oxidation increases in prediabetic patients and that there is a positive correlation between the disulfide and blood glucose and HbA1c levels [34].
Ateş et al., in another study, determined that thiol oxidation increases in Type 1 Diabetes Mellitus patients compared to the control group. In their study, they reported that an increase in oxide thiol form might be related to hyperglycemia and chronic inflammation [35].
In patients with autoimmune subclinical hypothyroidism, the native thiol level and native thiol/total thiol ratio were found to be lower in patients than in the control group. Moreover, TDH was reported to have shifted to disulfide formation in patients. Thyroid autoantibodies detected in autoimmune hypothyroditis were positively correlated with thiol oxidation [36].

CONCLUSION

Thiol/disulfide homeostasis is a novel and promising marker in the diagnosis of critical illnesses such as coronary artery disease, pulmonary embolism, endocrinological disorders, etc. Ungoing studies on its utility in clinical practice may introduce diagnostic and prognostic value in diseases in which antioxidants play a crucial role.

Declaration of Interest:
Authors declared no conflict of interests.

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