Total Thiols: Biomedical Importance And Their Alteration In Various Disorders

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Abstract:
Thiols are the organic compounds that contain a sulphhydryl group. Among all the antioxidants that are available in the body, thiols constitute the major portion of the total body antioxidants and they play a significant role in defense against reactive oxygen species. Total thiols composed of both intracellular and extracellular thiols either in the free form as oxidized or reduced glutathione, or thiols bound to proteins. Among the thiols that are bound to proteins, albumin makes the major portion of the protein bound thiols, which binds to sulphhydryl group at its cysteine-34 portion. Apart from their role in defense against free radicals, thiols share significant role in detoxification, signal transduction, apoptosis and various other functions at molecular level. The thiol status in the body can be assessed easily by determining the serum levels of thiols. Decreased levels of thiols has been noted in various medical disorders including chronic renal failure and other disorders related to kidney, cardiovascular disorders, stroke and other neurological disorders, diabetes mellitus, alcoholic cirrhosis and various other disorders. Therapy using thiols has been under investigation for certain disorders.

Key Words: Thiols, antioxidants, glutathione, free radicals, kidney diseases, cysteine-SH, γ-glutamyl cycle
Introduction to Thiols:

Thiols are a class of organic compounds that contain a sulphydryl group (–SH), also known as a thiol group, that is composed of a sulfur atom and a hydrogen atom attached to a carbon atom. Protein thiols in the plasma include the protein sulphydryl groups and protein mixed disulfides with homocysteine, cysteinylglycine, cysteine and glutathione. Human plasma contains homocysteine (HcySH), cysteinylglycine (CysGlySH), cysteine (CysSH), and glutathione (GSH) as reduced thiols. These thiols are also found as low-molecular-mass (symmetrical) disulfides, i.e., homocystine [(HcyS)2], cystinylglycine [(CysGlyS)2], cystine [(CysS)2], and glutathione disulfide (GSSG). In human plasma, concentration of protein sulphydryl groups (PSH) is in the 0.4–0.5 μM range, while that of low-molecular-mass thiols is in the 0.1–20 μM range.2,3

Within cells, the major low-molecular-weight sulphydryl/disulfide pool, GSH/GSSG, is principally in the reduced form. The CysSH/(CysS)2 pool, mainly in the disulfide form, quantitatively represents the largest pool of low-molecular-weight thiols and disulfides in plasma and the extracellular compartment on the whole. Therefore, intracellular proteins may be prevalently S-glutathionylated, while extracellular proteins may be predominantly S-cysteinylated. Plasma concentration of GSH is generally in the range of 2–4 μM2–4, CysSH is in the range of 8–10 μM, and that of (CysS)2 is higher than 40 μM.5

Protein Thiols:

Mammalian tissues are rich in protein thiols (20–40 mM) and many intracellular proteins have been identified that can undergo thiol group modification. The redox state of protein thiols is dependent on cellular function. Protein cysteines can be oxidised to free thiols, intra or interprotein disulfides, nitrothiols and sulphenic, sulphonic or sulphonic acids. In cytoplasm, the environment is highly reduced, mainly due to the high intracellular concentration of GSH and the GSH/GSSG ratio of 30-100. Hence, cysteins of cytoplasmic proteins are mainly present as free thiols. Extracellular proteins, in contrast, are mainly disulfide proteins due to the oxidative environment. Though proteins on plasma membrane are at the interface between an oxidising and reducing environment, many studies have shown the presence of exofacial protein thiols which are kept in reduced state by protein disulfide isomerases.6

Albumin is the most abundant protein in plasma and it makes up more than 50% of the total plasma protein. The total thiol status in the body, especially thiol (-SH) groups present on protein are considered as major plasma antioxidants in vivo and most of them are present over albumin, and they are the major reducing groups present in our body fluids. Cys-34 of albumin accounts for the bulk of free thiol (-SH) in plasma. About one-third of the albumin molecules in the plasma carry disulfide-bonded thiols at this Cys-34 residue. The pKa of the thiol group of Cys-34 is abnormally low (pKa = 5). This is in contrast to the pKa of most of the low molecular weight aminothiols present in plasma. Thus, at physiological pH, albumin-Cys34 exists primarily as thiolate anion and is highly reactive with metals, thiols, and disulfides.11 Metallothionein, a protein that binds 5–7 ions of metals such as Zn2+, Cu++, Cd2+, and Hg2+ via thiolate bonds, forms a significant proportion of total cell protein thiol. Albumin is also known to carry other thiols (e.g. glutathione and cysteinylglycine) along with other metabolites (e.g. nitric oxide) on Cys-34.

Glutathione:

Glutathione is a ubiquitous tripeptide, γ-glutamyl-cysteinyl glycine, found in most plants, microorganisms, and all mammalian tissues. Glutathione exists in two forms the thiol-reduced (GSH) and disulfide oxidised (GSSG).11 Eukaryotic cells have three major reservoirs of GSH, cytosol (90%), mitochondria (10%) and small percentage in the endoplasmic reticulum.15,16 The γ-glutamyl linkage promotes intracellular stability and the sulfhydryl group is required for GSH’s functions. The peptide bond linking the amino-terminal glutamate and the cysteine residue of GSH is through the γ-carboxyl group of glutamate through the conventional α-carboxyl group. This unusual arrangement resists degradation by intracellular peptidases and is subject to hydrolysis by only one known enzyme, γ-glutamyltranspeptidase (GGT), which is on the external surfaces of certain cell types. Furthermore, the carboxyl-terminal glycine moiety of GSH protects the molecule against cleavage by intracellular γ-glutamylcyclotransferase. As a consequence, GSH resists intracellular degradation and is only metabolized extracellularly.

GSH as cysteine storage and the γ-glutamyl cycle

Homocysteine is situated at a critical regulatory branch point in sulfur metabolism. It can be remethylated to methionine, an important amino acid in protein synthesis, or converted to cysteine in the transsulfuration pathway.17–19 Cysteine is the only thiol-containing amino acid in proteins. The metabolism of it is complex and is still incompletely understood.17 Its degradation proceeds by several pathways leading to formation of taurine or inorganic sulfate.20 One of the major determinants of the rate of GSH synthesis is the availability of cysteine. Cysteine is normally derived from the diet and protein breakdown, and in the liver from methionine via the transulfuration pathway.17,19 Cysteine differs from other amino acids because its sulfhydryl form, cysteine, is predominant inside the cell whereas its disulfide form, cystine, is predominant outside the cell. Cysteine readily autoxidizes to cystine in the extracellular fluid; once it enters the cell, cystine is rapidly reduced to cysteine. Therefore, the key factors that regulate the hepatocellular level of cysteine other than diet include membrane transport of...
cysteine, cysteine, and methionine as well as the activity of the transulfuration pathway. \(^{21-23}\) Although glutamate and glycine are also precursors of GSH, there is no evidence to suggest that their transport influences GSH synthesis since they are synthesized via several metabolic pathways within hepatocytes. \(^{21}\)

One of the most important functions of GSH is to store cysteine because cysteine is extremely unstable extracellularly and rapidly auto-oxidizes to cystine, in a process producing potentially toxic oxygen free radicals. \(^{24}\) Cysteine also is needed for glutathione synthesis and provides its thiol residue. \(^{25}\) Synthesis of glutathione takes place in two steps. At first, γ-glutamylcysteine synthetase couples glutamate to cysteine forming γ-glutamlycysteine. The availability of cysteine is regulatory in that step. Glutathione is then directly synthesized by coupling γ-glutamlycysteine to glycine catalyzed by glutathione synthetase. \(^{24,26}\) The γ-glutamyl cycle allows GSH to serve as a continuous source of cysteine. GSH is released from the cell by carrier-mediated transporters \(^{27}\) and the ectoenzyme GGT then transfers the γ-glutamyl moiety of GSH to an amino acid (the best acceptor being cystine), forming γ-glutamyl amino acid and cysteinylglycine. The γ-glutamyl amino acid can then be transported back into the cell to complete the cycle.

Once inside the cell, the γ-glutamyl amino acid can be further metabolized to release the amino acid and S-oxoproline, which can be converted to glutamate and used for resynthesis of GSH. Cysteinylglycine is broken down by dipeptidase to generate cysteine and glycine. Cysteine is readily taken up by most if not all cells. Once inside the cell, the majority of cysteine is incorporated into GSH; some is incorporated into protein, depending on the need of the cell, and some is degraded into sulfate and taurine. For most cells, this mechanism provides a continuous source of cysteine. Thus, the γ-glutamyl cycle allows the efficient utilization of GSH as cysteine storage. \(^{24}\)

In the human body, glutathione has diverse important functions such as storage and transport of cysteine, maintaining the reduced state of proteins and thiols, and protecting cells from toxic compounds such as reactive oxygen species, drugs, or heavy metal ions. \(^{24,26}\) Two different types of detoxification enzymes need glutathione as a substrate. Glutathione peroxidases catalyze the reaction of glutathione with (oxygen) free radicals, whereby glutathione is oxidized. Subsequently, the inactive oxidized form of glutathione can be reduced again by glutathione reductase. Glutathione S-transferases catalyze the conjugation between glutathione and toxic compounds. That glutathione conjugate is then excreted and additional glutathione has to be synthesized. Antioxidants, including GSH, have been shown to protect against or delay apoptosis triggered by many different stimuli. \(^{25,26}\) One study has shown that the protective effect of thiol agents may be related to down-regulation of Fas expression on T lymphocytes rather than their antioxidative properties. \(^{30}\)

It has been shown that there is accelerated GSH efflux from the cell stimulated to undergo apoptosis with different proapoptotic stimuli \(^{27,28,31} \) and depletion of cell GSH will facilitate apoptosis to occur, provide antioxidants extracellularly, and possibly stimulate phagocytic cells to engulf the apoptotic cell. \(^{25}\) Mixed disulfides with proteins are formed by reaction of S-thiolation, in which protein thiols conjugate with non-protein thiols. \(^{25}\) This process plays a regulatory and an antioxidant role, since it protects protein–SH groups against irreversible oxidation to –SO\(_2\)H and –SO\(_3\)H, and, on the other hand, it participates in signal transduction. \(^{33}\) Redox state of these surface thiols regulates platelet aggregation, HIV-1 entry, \(^{34}\) integrin mediated adhesion, \(^{35}\) and receptor shedding. \(^{36}\) The regulatory and antioxidant action of S-thiolation is closely connected with dethiolation via the reduction of disulfides catalyzed by thioltransferases, thioredoxin and glutaredoxin. \(^{37,38}\)

**Oxidative stress and thiol status**

Under conditions of moderate oxidative stress, oxidation of Cys residues can lead to the reversible formation of mixed disulfides between protein thiol groups and low–molecular-mass thiols (S-thiolation), particularly with GSH (S-glutathionylation). Protein S-glutathionylation can directly alter or regulate protein function (redox regulation) and may also have a role in protection from irreversible (terminal) oxidation. S-glutathiolation of protein cysteine residues protects against higher oxidation states of the protein thiol, thereby preserving the reversibility of this type of modification. Second, reduced protein thiols can be regenerated from their S-glutathiolated forms enzymatically through the action of protein disulfide isomerase, mitochondrial glutaredoxin, or thioredoxin. Protein S-glutathiolation has also been implicated in the control of ubiquitination, the binding of transcription factor c-Jun to DNA, and sarcoplasmic Ca\(^{2+}\)-ATPase activity. \(^{39}\)

S- Glutathionylated proteins accumulate under oxidative/ nitratosive stress conditions, but they can be readily reduced to free thiol groups when normal cellular redox status is recovered by glutaredoxins (thioltransferases) or reducing agents. A characteristic hallmark of many pathophysiologic conditions is a decrease in the GSH: GSSG ratio. When GSSG accumulates in cells, it can undergo disulfide exchange reactions with protein thiols, leading to their S-glutathionylation. S-Glutathionylated proteins have been investigated as possible biomarkers of oxidative/nitratosive stress in some human diseases, such as renal cell carcinoma and diabetes. Glutathionylated hemoglobin is increased in patients with type 1 and type-2 diabetes, hyperlipidemia, and uraemia associated with haemodialysis or peritoneal dialysis. \(^{40}\)
Thioredoxin, an enzyme ubiquitously expressed in endothelial cells and medial smooth muscle cells, is a major cytosolic protein thiol reductant and appears to be a target for ROS with implications for cell signalling.\(^4\) Reversibility of the oxidation-mediated protein modification can be achieved via the action of another enzyme, glutaredoxin.\(^4\) Protein thiols represent a prominent biological target for reactive nitrogen species (RNS) involved in cell signalling within the vasculature and many other tissues. S-nitrosation of protein cysteine residues is a motif for –NO related signalling. Selectivity in the S-nitrosation of protein thiols represents a means for allosteric control of protein function.\(^5\)

The chemical modification of protein thiols by ROS and RNS does not occur in isolation. Considering its relative abundance, it is not surprising that GSH functions as a prominent reconstituent for protein thiol modification in the face of ROS and RNS. It has been estimated that proteins can scavenge the majority (50%–75%) of reactive species generated\(^6\) and much of this function is attributed to the thiol groups present on them. The serum levels of protein -SH in the body indicate antioxidant status and low levels of protein -SH correlated positively with the increased levels of lipid peroxides\(^7\) and of advanced oxidation protein products (AOPPs).\(^8\)

**Thiol status in various disorders:**

Hypertension and cardiovascular disorders: The biological effects of nitric oxide (NO) are in large part mediated by S-nitrosylation of peptides and proteins to produce bioactive S-nitrosothiols (SNOs).\(^9\)\(^-\)\(^16\) The observation of abnormal SNO levels in numerous pathophysiological states\(^17\) suggests that dysregulation of SNO homeostasis may contribute to disease pathogenesis. For example, the hypotension of human sepsis is accompanied by increases in circulating levels of vasodilatory SNOs.\(^18\) Gandley et al\(^19\) have shown that the buffering function of SNO-albumin is impaired in preeclamptic patients, where the thiol of albumin acts as a sink for NO and thus, raises blood pressure. Gandley et al extend this paradigm by proposing that a defect in SNO turnover contributes to the hypertension of preeclampsia.

In the blood, S-nitrosoalbumin (SNO-albumin) and S-nitrosohemoglobin (SNO-Hb) constitute the major conduits for circulating NO bioactivity. Although both SNOs may influence blood pressure, they operate within distinct signaling circuits. SNO-Hb can be viewed as a principal regulator of SNO homeostasis, adaptively modulating NO chemistry to control NO bioactivity. In contrast, it appears that rather than transducing a specific signal, albumin operates as a buffer to maintain NO homeostasis.\(^20\) S-nitrosylation of albumin occurs at Cys-34 via reactions—with NO or nitrosothiols—that are favored by design: specifically, both hydrophobic pockets in albumin (NO/O2 coupling) and bound copper (NO/metal redox coupling) may serve to generate nitrosylating species.\(^21\)\(^-\)\(^24\) Gandley et al\(^25\) make the case that the buffering function of SNO-albumin is impaired in preeclamptic patients, where the thiol of albumin acts as a sink for NO and thus, raises blood pressure. Redistribution of NO, from the tissues into the hydrophobic core of the protein, subserves S-nitrosylation and lowers the steady-state level of vasodilatory NO within the vascular smooth muscle.\(^26\) Accumulating evidence strongly suggests a role of SNOalbumin in mitigating cardiovascular risk.

In women with preeclampsia, homocysteine and cysteine levels, which are lowered in normotensive pregnancy, were comparable to levels in nonpregnant women, whereas glutathione levels were lower. Those results suggest that in women with preeclampsia, glutathione use is higher or its synthesis is disturbed. Therefore, glutathione might affect pathophysiology of preeclampsia.\(^27\) Zhang et al\(^28\) demonstrate regulation by a mitochondria-specific thioredoxin, which reduces oxidative stress and increases NO bioavailability, thus preserving vascular endothelial cell function and preventing atherosclerosis development. It has been shown that LDL oxidation by L-cysteine and Cu\(^2+\) requires superoxide but not hydrogen peroxide or hydroxyl radical. The reaction may involve the metal ion-dependent formation of L-cysteine radical anion which is oxidized by oxygen yielding superoxide and the disulfide. LDL modified by L-cysteine and smooth muscle cells exhibited similar physical and biological properties, indicating that thiol-dependent superoxide generation may be the oxidative mechanism in both the systems. Thiols also promote superoxide independent lipid peroxidation but human macrophages fail to rapidly degrade these oxidized LDLs.\(^29\)

**In Kidney Diseases:** Presence of oxidative stress in renal failure is well proved and the several studies have shown decreased levels of thiol status in chronic renal failure (CRF).\(^30\)\(^-\)\(^34\) Increased presence of ROS generated in these patients are believed to consume the available thiol groups. Studies have also shown negative correlation of serum creatinine with the protein thiols,\(^35\) indicating increased protein SH consumption with increase in severity of renal failure.\(^36\) Albumin provides the bulk of the total serum thiols\(^36\)\(^,\)\(^39\) and loss of albumin in the urine of CRF patients, logically, should increase thiol groups in urine. Contrary to this, a study has shown significantly low levels of urinary protein thiols.\(^40\) The authors have also shown significant decrease in serum albumin and protein-bound thiol groups in CRF patients. These findings suggest that the albumin excreted in the urine is deficient in thiol groups.

The decrease in protein thiols in the urine of CRF patients could be because of increased oxidation of albumin-bound thiol groups in the serum.\(^41\)\(^,\)\(^45\) Excretion of such albumin, deficient in the reduced form of thiol groups, in the urine decreases the levels of protein-
bound thiols in urine. There occurs a significant decrease in urinary thiols in patients with proteinuria and it varies with the amount of protein excreted in urine. There was also a significant decrease in plasma protein thiol levels in pediatric nephrotic syndrome, primary glomerular diseases, moderate to severe chronic kidney disease, end stage renal disease, systemic lupus erythematosus (SLE) with and without nephritis. It was seen that when the sodium consumption was increased, the serum protein thiols were found to be decreased.

**Gastro Intestinal Diseases:** Oxidative stress gets exacerbated by pro-oxidants such as various drugs including alcohol. Ingested alcohol besides producing striking metabolic imbalances in the liver, also leads to the formation of reactive oxygen species (ROS). The levels of serum protein thiols were found to be decreased in alcohol abusers. Synthesis of glutathione and cysteine mainly occurs in hepatocytes, whereas most other tissues are supplied with these thiols via sinusoidal efflux into the blood. Since canicular efflux also occurs, thiols may be present in human bile. However, thiol composition of human gallbladder bile is largely unknown, which makes it difficult to speculate on the exact function of thiols in bile.

Variation in non protein thiol levels was found in human gall bladder bile of patients with most of the thiols in their oxidized forms which may indicate the presence of considerable chemical or oxidative stress. Also, inflammatory and oxidative events have remarkable importance in bladder cancer. Patients with bladder cancer were found to have significantly lower levels of total thiols and protein bound thiol groups, the levels were much lower in invasive type. Therefore, thiols are present in considerable amounts in human gallbladder bile of patients with various gastrointestinal disorders, with most of the thiols in their oxidised forms, which may indicate the presence of considerable chemical or oxidative stress in the patients. Previous studies have also suggested that Helicobacter pylori (H. pylori) infection may play an important role in the process of atherosclerosis. Serum -SH levels were significantly lower in H. pylori positive group than H. pylori negative group.

**Diabetes mellitus and other disease conditions:** Free radical mediated oxidative stress has been implicated in the pathogenesis of diabetes mellitus (DM) and its complications. Serum protein thiols have been found to be decreased in both types of diabetes mellitus. These decreases were partially explained by metabolic-, inflammatory- and iron alterations. Serum protein thiols have been found to be decreased in patients with complications of type 2 diabetes mellitus. There have been reports on decreased plasma thiol levels in diabetic patients recently. Significant decrease in P-SH levels in diabetic hemodialysis (DHD) patients compared with the level in healthy participants and DM patients. While there was no significant difference in the whole blood GSH levels between the DM patients and controls. It was significantly higher in DHD patients in comparison to the DM patients. The low P-SH level in DHD patients, but not in DM patients, suggests that dialysis is responsible for this decrease.

A significant increase in free iron in Fe³⁺ state with a decrease in protein thiols has been shown in diabetic cases under poor glycemic control. The finding that thiols as facile targets of glycation and low molecular mass thiols as potent glycation inhibitors, may aid the design of therapeutic agents for the treatment of the complications of diabetes. Elevated glucose levels can induce oxidative stress in gestational diabetes (GDM) mothers. This may be due to the increased oxidative stress prevalent in GDM. A significant increase in the erythrocytic GSH and protein thiols in GDM maternal blood when compared to controls have been observed. Cord blood levels of protein thiols were also significantly increased in GDM This may be in response to the milieu of increased oxidative stress in case of GDM cord blood and oxidative stress in the fetus induced by GDM.

Human amylyn (hA) is a small fibrillogenic protein that is the major constituent of pancreatic islet amyloid, which occurs in most subjects with type-2 diabetes mellitus. There is growing evidence that hA toxicity towards islet b-cells is responsible for their gradual loss of function in type-2 diabetes mellitus. Preventing hA-mediated cytotoxicity has been proposed as a route to halt the progression of this disease, although this has not yet been demonstrated in vivo. The thiol antioxidants, N-acetyl-L-cysteine (NAC), GSH and dithiothreitol, which not only react with ROS, but also modulate the cellular redox potential by increasing intracellular levels of GSH and/or by acting as thiol reducing agents, afford almost complete protection and inhibit the progression of hA-evoked apoptosis. These results indicate that, in addition to the induction of oxidative stress, hA appears to mediate cytotoxicity through signalling pathways that are sensitive to the actions of thiol antioxidants.

**Other disorders:** A significant fall in plasma protein thiols have also been observed after the assisted reproduction procedures like intrauterine insemination, indicating increased oxidative stress after the procedure. Oxidative stress has been implicated in the degeneration of dopaminergic neurons in the substantia nigra (SN) of Parkinson's disease (PD) patients. An important biochemical feature of presymptomatic PD is a significant depletion of the thiol antioxidant glutathione (GSH) in these neurons resulting in oxidative stress, mitochondrial dysfunction, and ultimately cell death. In schizophrenic patients, the amount of homocysteine in plasma was higher compared and the level of GSH, C-SH and CG-SH was decreased. This indicates that ROS and RNS may stimulate oxidative/nititative modifications of plasma proteins in schizophrenic patients. In apoptosis, generation of
oxidative stress, leads to perturbation of protein thiols. The role of oxidative stress has been studied in rheumatoid arthritis (RA) and other inflammatory joint diseases including psoriatic arthritis (PsA). A biochemical disturbance of plasma sulphydryl/disulfides balance is observed in patients with RA compared to controls with an increase in some oxidised forms (disulfides and protein mixed disulfides) and a decrease in free thiols. The increase in total homocysteine, correlated to the higher risk of cardiovascular diseases in RA patients, is associated with higher levels of the oxidised forms, disulfides and protein-thiol mixed disulfides. The SH levels in synovial fluid were significantly lower in patients affected by PsA and rheumatoid arthritis compared to Osteo Arthritis (OA). The serum SH levels in PsA were lower than OA and higher than RA patient. Low levels of free thiol groups have been observed in Henoch-Schönlein purpura. Ankylosing spondylitis (AS) is a chronic inflammatory disease where neutrophil activation-mediated oxidative stress may also have an important role in the pathogenesis of AS. Therefore, the importance of neutrophil activation as the main source of oxidative stress was investigated in patients with AS and was found to be decreased in thiol levels in the total AS patient group. Wilson's disease (WD) is an inherited disorder characterized by selective copper deposition in liver and brain, chronic hepatitis and extra-pyramidal signs. There was a decrease of protein-thiols, GSH/GSSG ratio in the liver and striatum. There was a decrease of protein-thiol oxidation and lipid peroxidation in patients with uremia. Total thiol levels were significantly lower in patients with osteoarthritis. The role of oxidative stress has been studied in rheumatoid arthritis (RA) and other inflammatory joint diseases including psoriatic arthritis (PsA). A biochemical disturbance of plasma sulphydryl/disulfides balance is observed in patients with RA compared to controls with an increase in some oxidised forms (disulfides and protein mixed disulfides) and a decrease in free thiols. The increase in total homocysteine, correlated to the higher risk of cardiovascular diseases in RA patients, is associated with higher levels of the oxidised forms, disulfides and protein-thiol mixed disulfides. The SH levels in synovial fluid were significantly lower in patients affected by PsA and rheumatoid arthritis compared to Osteo Arthritis (OA). The serum SH levels in PsA were lower than OA and higher than RA patient. Low levels of free thiol groups have been observed in Henoch-Schönlein purpura. Ankylosing spondylitis (AS) is a chronic inflammatory disease where neutrophil activation-mediated oxidative stress may also have an important role in the pathogenesis of AS. Therefore, the importance of neutrophil activation as the main source of oxidative stress was investigated in patients with AS and was found to be decreased in thiol levels in the total AS patient group. Wilson's disease (WD) is an inherited disorder characterized by selective copper deposition in liver and brain, chronic hepatitis and extra-pyramidal signs. There was a decrease of protein-thiols, GSH/GSSG ratio in the liver and striatum. Hence, it is assumed that enhanced oxidative stress may play a central role in the cell degeneration in WD, at the main sites of copper deposition.

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