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Mini Review

Glutathione's Role in Oxidative Stress and Bone Health: Implications for Osteoporosis

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Numerous cells, including erythrocytes, hepatocytes, and cardiomyocytes, contain the thiol tripeptide glutathione (GSH) [1], which is made up of 3 amino acids, l-glutamyl, l-cysteinyl, and glycine [2]. 90% of GSH is found in the cytoplasm, and a significant fraction is also present in the mitochondria and endoplasmic reticulum (ER) [1]. GSH exhibits diversity in its functions, ranging from a major non-enzymatic scavenger of cellular redox state to involvement in cell signaling, proliferation, and differentiation [3]. GSH exists in two forms, oxidized GSH(GSSG) and reduced GSH [4]. GSH performs its protective role with the help of two enzymes, glutathione peroxidase and glutathione reductase [1] (Figure 1).

GSH has various roles in maintaining cellular oxidative stress, regulating certain enzymatic activities, influencing gene expression, and promoting cell differentiation and proliferation, among others [5]. This essential endogenous antioxidant, which cells make, actively contributes to the elimination of free radicals and reactive oxygen species [6]. All of the biological activities of the GSH molecule depend on the redox state of the thiol moiety [7]. Severe oxidative stress damages protein functioning by irreversibly oxidizing the thiol residues [3].

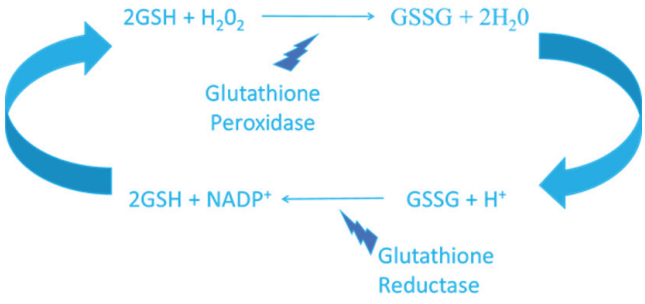

Figure 1: Interconversion of different forms of glutathione.

GSH levels are regarded as a significant indicator of oxidative stress in a cell [1]. Intracellular GSH depletion is regarded as an early step of apoptosis as it occurs before loss of mitochondrial integrity, cytochrome c release, and activation of caspases [8]. GSH depletion is also linked to necroptosis, a different type of programmed cell death, characterized by distinctive features in the mitochondria, lysosomes, and plasma membrane [9]. Cells with necroptosis exhibit translucent cytoplasm, swollen organelles, larger cell volume, and breakdown of the plasma membrane [10]. Ferroptosis is a type of programmed cell death that differs from other types of cell death in terms of morphology, biochemistry, and genetics. It also occurs by GSH deprivation and is characterized by iron dependence and lipid ROS [11].

Effect of GSH on bone metabolism in the postmenopausal period

ROS production has long been linked to bone remodeling [12], but excessive ROS due to either estrogen deficiency [13], a lack of antioxidants in the diet [14], or secondary to other diseases can disrupt normal bone remodeling and lead to osteoclastogenesis [15]. The primary pathway for osteoblast destruction via ROS involves mitochondrial apoptosis [16], which occurs through increased membrane permeability, release of cytochrome c, and apoptosis-inducing factor [17]. ROS also promotes osteoclast differentiation through multiple pathways, including MAPK, IP3, and NFkB [18], leading to osteoclast maturation via activation of genes like NFATC1 [19]. An animal study showed bone loss associated with oxidative stress in ovariectomized mice compared to healthy controls [20]. Another study found increased osteoclast

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activity when human bone marrow cells were exposed to ROS, while treatment with antioxidants reduced osteoclast proliferation and differentiation [21]. A recent study linked reduced GSH levels with decreased bone mineral density in Asian women [22]. Similarly, another study reported lower serum GSH levels in women with postmenopausal osteoporosis [23]. Postmenopausal women exhibited significantly lower plasma GSH levels than perimenopausal women; this decline suggests oxidative stress after menopause [22]. The drop in GSH levels following menopause, even minor deviations, can trigger osteoporosis. A recent study on insomnia in peri- and postmenopausal women observed a significant decrease in GSH levels among postmenopausal participants [24]. Another study noted decreased antioxidant activity of GSH in postmenopausal women compared to perimenopausal women, differing from the present study, which measured blood levels of oxidized GSH [25], whereas the current study assessed plasma levels of reduced GSH, responsible for GSH's potent effects. This study also found a significant inverse correlation between GSH and asprosin and a significant positive correlation with OPG [26-33].

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