# GLUTATHIONE PEROXIDASE 4 (GPX4) IN SUBCLINICAL HYPOTHYROIDISM: LINKING OXIDATIVE STRESS AND THYROID DYSFUNCTION

**Taranvirinderdeep Singh[1], Diksha[2]**
School of Pharmacy, Desg Bhagat University, Mandi Gobindgarh, Punjab, India

**ABSTRACT**

Subclinical hypothyroidism (SCH) is defined by elevated thyroid-stimulating hormone (TSH) levels with normal circulating thyroid hormones and is associated with increased cardiovascular risk and metabolic disturbances. A pivotal, yet underexplored, aspect of SCH pathophysiology is oxidative stress (OS):- an imbalance between reactive oxygen species (ROS) production and antioxidant defenses. The thyroid gland is particularly susceptible to oxidative damage due to its high oxidative environment needed for hormone synthesis. Glutathione peroxidase 4 (GPX4), a selenium-dependent selenoenzyme, is critical for neutralizing lipid peroxides and protecting thyrocytes from ROS-induced injury and ferroptotic cell death. Impaired GPX4 activity, often linked to selenium deficiency or persistent OS, may exacerbate thyroid dysfunction, suggesting a mechanistic link between redox imbalance and the evolution of SCH. While animal studies and indirect clinical evidence highlight reduced GPX4 expression and altered selenium status in thyroid disorders, direct clinical correlations in SCH remain limited. Elucidating GPX4's role in thyroid redox biology could enhance early diagnosis, enable risk stratification, and inform personalized interventions, such as targeted antioxidant or micronutrient supplementation. This review underscores the need for integrative clinical studies to clarify GPX4's functional significance in SCH and explores its therapeutic potential in mitigating progression to overt hypothyroidism.

**KEY WORDS:** Subclinical hypothyroidism (SCH), Reactive Oxygen Species (ROS), Glutathione peroxidase 4 (GPX4), oxidative stress (OS), hydrogen peroxide ($H_2O_2$)

## INTRODUCTION

Subclinical hypothyroidism (SCH) is characterized by elevated thyroid-stimulating hormone (TSH) levels with normal circulating thyroid hormone concentrations. Although often asymptomatic, SCH has been increasingly recognized for its association with adverse cardiovascular risk and metabolic disturbances, mirroring some of the complications seen in overt hypothyroidism [1]. A central pathological feature in both overt and subclinical hypothyroidism is a disturbance in oxidative stress (OS) homeostasis, driven primarily by an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense capacity [2].

Oxidative stress in thyroid dysfunction arises due to the gland's inherently high oxidative environment, required for hormone synthesis, but which also predisposes thyroid tissue to oxidative damage when antioxidant defenses are compromised [3]. This imbalance is exacerbated in hypothyroid states, including SCH, primarily due to a decreased efficacy of the intrinsic antioxidant systems, resulting in the accumulation of ROS, increased lipid peroxidation, and cellular injury [4].

Glutathione Peroxidase 4 (GPX4), a crucial selenoenzyme, plays a central role in neutralizing lipid peroxides and protecting cells from oxidative damage-its function is especially vital in tissues prone to lipid peroxidation, such as the thyroid gland [5]. By reducing phospholipid hydroperoxides within biological membranes, GPX4 limits ferroptosis, an iron-dependent form of cell death induced by excessive membrane lipid peroxidation. GPX4 impairment not only amplifies oxidative injury but may also contribute to thyroid cell dysfunction and altered hormone production [6]. The interaction between GPX4 activity and oxidative stress in subclinical hypothyroidism presents a compelling mechanistic link: insufficient antioxidant protection allows ROS accumulation, damaging thyroid cells and potentially perpetuating thyroid hormone dysregulation [3, 7]. This connection underscores the significance of antioxidant systems, such as GPX4, in the maintenance of thyroid health and highlights the potential for therapeutic interventions aimed at restoring redox balance in SCH [8].

## PATHOPHYSIOLOGY OF SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism (SCH) is defined by elevated serum thyroid-stimulating hormone (TSH) levels with normal concentrations of free thyroxine (FT4) and triiodothyronine (FT3) [1]. Although often considered a mild or early form of hypothyroidism, SCH involves several complex physiological and biochemical alterations that may contribute to significant clinical consequences over time [9]. The condition reflects a compensatory mechanism by the hypothalamic-pituitary-thyroid (HPT) axis in response to minimal or early thyroid hormone deficiency at the tissue level [10]. This leads to elevated TSH secretion despite circulating FT3 and FT4 being within normal ranges, suggesting that peripheral tissues may still be experiencing a relative hypothyroid state [11].

The early dysfunction of the thyroid gland in SCH is frequently attributed to autoimmune thyroiditis, particularly Hashimoto's thyroiditis, wherein chronic lymphocytic infiltration results in gradual destruction of thyroid follicular cells [12]. Other causes include iodine imbalance, post-thyroidectomy status, and radioiodine therapy. In autoimmune cases, the presence of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies leads to progressive inflammation, cellular damage, and impaired hormone synthesis, even before clinical symptoms or significant hormone imbalances manifest [13].

At the cellular level, thyrocytes (thyroid follicular cells) are metabolically active and require reactive oxygen species (ROS) such as hydrogen peroxide (H?O?) for the iodination of thyroglobulin during thyroid hormone synthesis [14]. However, this redox-intensive environment makes the gland particularly vulnerable to oxidative stress. In SCH, elevated TSH itself may contribute to increased ROS production through activation of NADPH oxidase. Without sufficient antioxidant defense mechanisms, this accumulation of ROS can lead to lipid peroxidation, mitochondrial dysfunction, and eventual thyrocyte injury [15]. These early redox imbalances are believed to precede overt hormone depletion and contribute to the pathogenesis of SCH [16].

Oxidative stress not only impacts the thyroid gland locally but may also contribute to systemic effects observed in SCH, such as dyslipidemia, endothelial dysfunction, subtle neuropsychiatric symptoms, and reproductive irregularities [17]. These effects are thought to arise from tissue-level hypothyroidism, inflammatory signaling, and compromised mitochondrial energy metabolism [18]. Moreover, patients with SCH-especially those with high TSH levels (>10 mIU/L) or elevated anti-TPO antibodies-are at a greater risk of progressing to overt hypothyroidism [19]. Chronic oxidative stress and inflammation may accelerate this progression by further damaging thyroid architecture and impairing hormonal feedback regulation [20].

Importantly, antioxidant enzymes such as Glutathione Peroxidase 4 (GPX4) may play a critical role in modulating oxidative stress within the thyroid. GPX4 protects cells by reducing lipid hydroperoxides and inhibiting ferroptosis-a form of iron-dependent, oxidative cell death [6, 21]. A deficiency or downregulation of GPX4 activity, which may occur due to selenium insufficiency or chronic oxidative burden, could exacerbate thyrocyte injury and promote the development or worsening of SCH [22]. Thus, oxidative stress and inadequate antioxidant responses are central to the early pathophysiological changes in SCH, providing a mechanistic link between cellular redox balance and thyroid dysfunction [23]

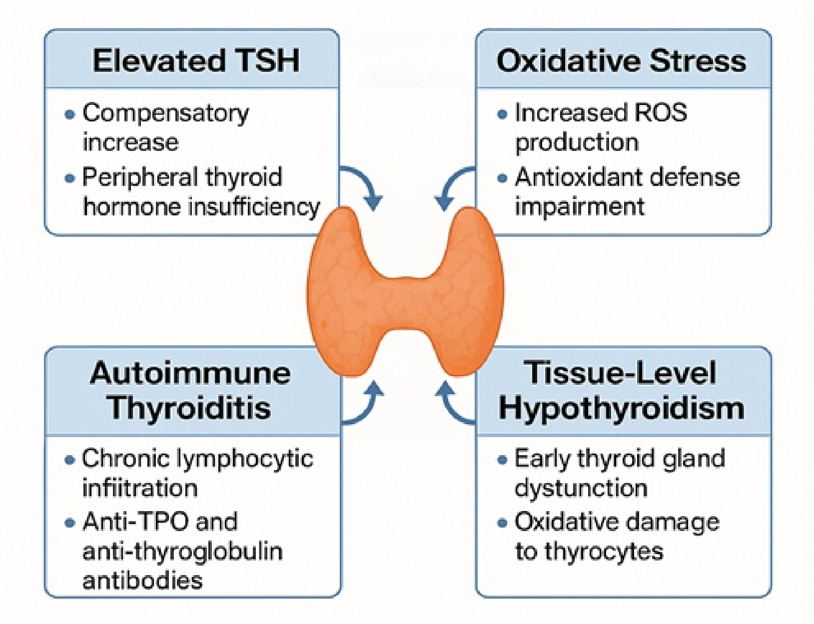


**Figure 1: Pathophysiology of Subclinical Hypothyroidism .**
**OXIDATIVE STRESS IN THYROID DYSFUNCTION**
**Generation of Reactive Oxygen Species (ROS) in Thyroid Cells**

With regards to thyroid homeostasis, the reactive oxygen species (ROS) pathway is central. TH enhances intracellular energy requirement all the time it increases mitochondrial oxidative phosphorylation, and hence the level of ROS- an obligatory by-product of the synthesis of TH [25]. One of the main ROS, hydrogen peroxide (H 2 O 2), is required in the thyroid peroxidase (TPO) catalyzed iodination of the thyroglobulin and hence endogenous biosynthesis of thyroid hormone [14]. Beyond the physiological boundaries, a ROS over production or deficiency in antioxidant barriers could result in oxidative damage in the thyroid follicular compartment, reduced activity of TPO, and a resultant alteration of thyroid hormones synthesis [26].

**ROLE OF OXIDATIVE STRESS IN THYROID TISSUE DAMAGE**

The dis-balance of proliferation of the reactive oxygen species (ROS) and cell antioxidant defences leads to oxidative stress (OxS), the disease that may impair cell integrity, which is caused by devastating lipid membranes, proteins, and DNA [27]. In the thyroid, an increased amount of ROS interferes with the synthesis of hormones, changes the cellular constituent, and induces inflammation [7, 17]. Hypothyroidism and hyperthyroidism can increase OxS; the former can do it through the reduction of the antioxidant capacity, and the latter increases ROS production [28]. The contribution to the pathogenesis and severity of thyroid dysfunction is thus by OxS-mediated tissue damage [29].

**ROS AND AUTOIMMUNE THYROIDITIS**

Autoimmune thyroid diseases (Autoimmune thyroiditis) such as Hashimoto Thyroiditis (HT) are characterized by immune cell influx to the thyroid and subsequent inflammatory changes in the tissue [30]. This inflammatory environment in combination with increased reactive oxygen species (ROS) enhances tissue damage and impairment [31]. In HT, the production of inflammatory cytokines, especially IL-23 induces production of ROS in the thyroid follicular cells, creating an inflammation-oxidative damage-related feedback loop. This type of cyclical destruction adds to the rapid destruction of papillary like thyroid. Besides, ROS induces the transcription of adhesion molecules on the thyroid cells thereby increasing their susceptibility to the autoimmune assault [32].

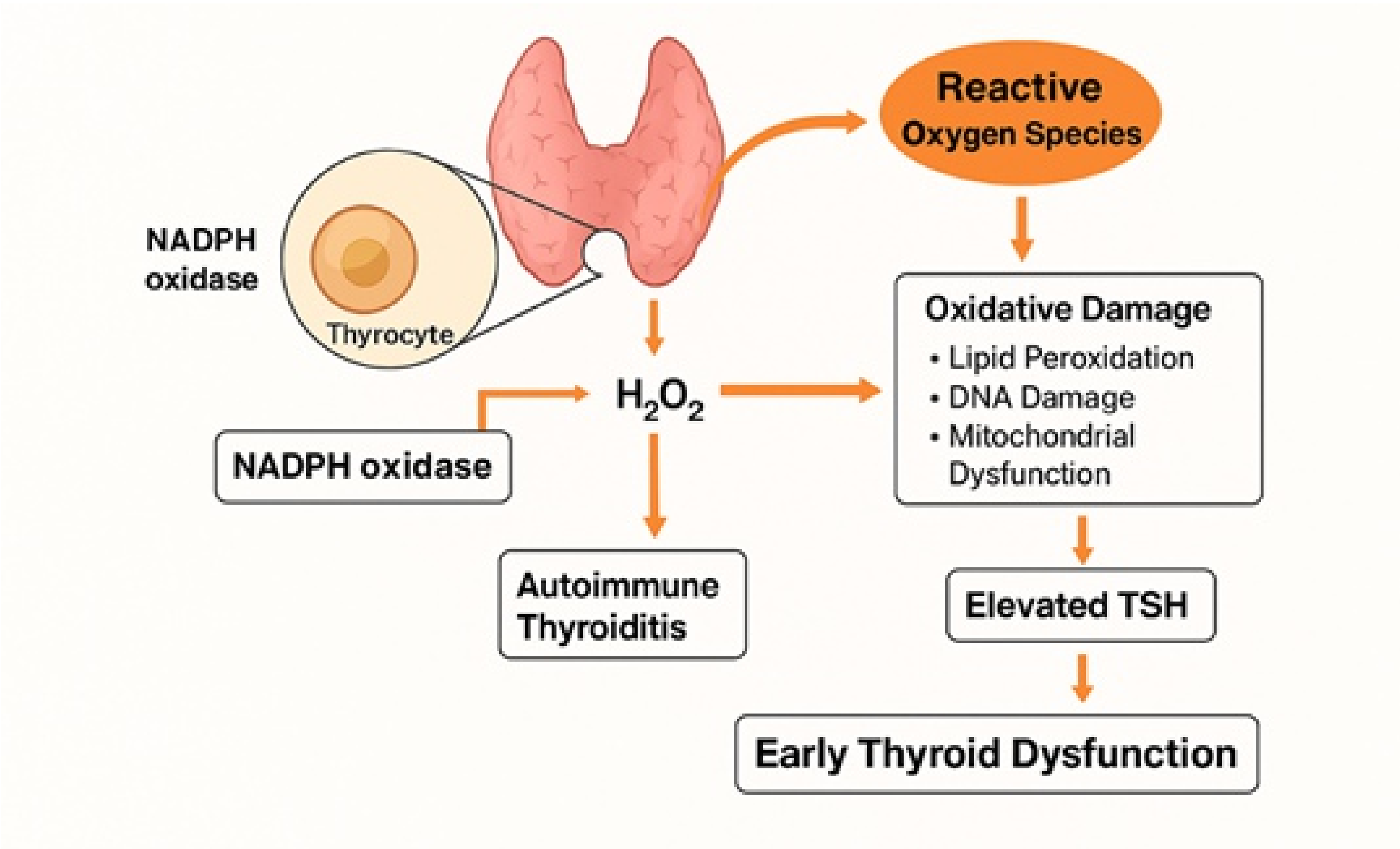


**Figure 2: Oxidative stress in thyroid gland**
**Generation and effects of ROS in thyroid tissue and their role in early thyroid dysfunction — .**

## OVERVIEW OF GPX4: STRUCTURE AND FUNCTION

GPX4 Gene and Protein Structure

Gene: The GPX4 gene encodes glutathione peroxidase 4, part of the glutathione peroxidase family. It is a selenoprotein, meaning its active site includes the rare amino acid selenocysteine, inserted via specialized translation of the UGA codon and a SECIS element in its mRNA [5].

Protein: The protein is unique among GPX family members: It is largely monomeric (unlike the tetrameric structure of GPX1/GPX3). The catalytic triad involves selenocysteine, glutamine, and tryptophan. The monomer's structure allows direct access for membrane-incorporated hydroperoxides. Alternative splicing results in cytosolic, mitochondrial, and nuclear isoforms [34].

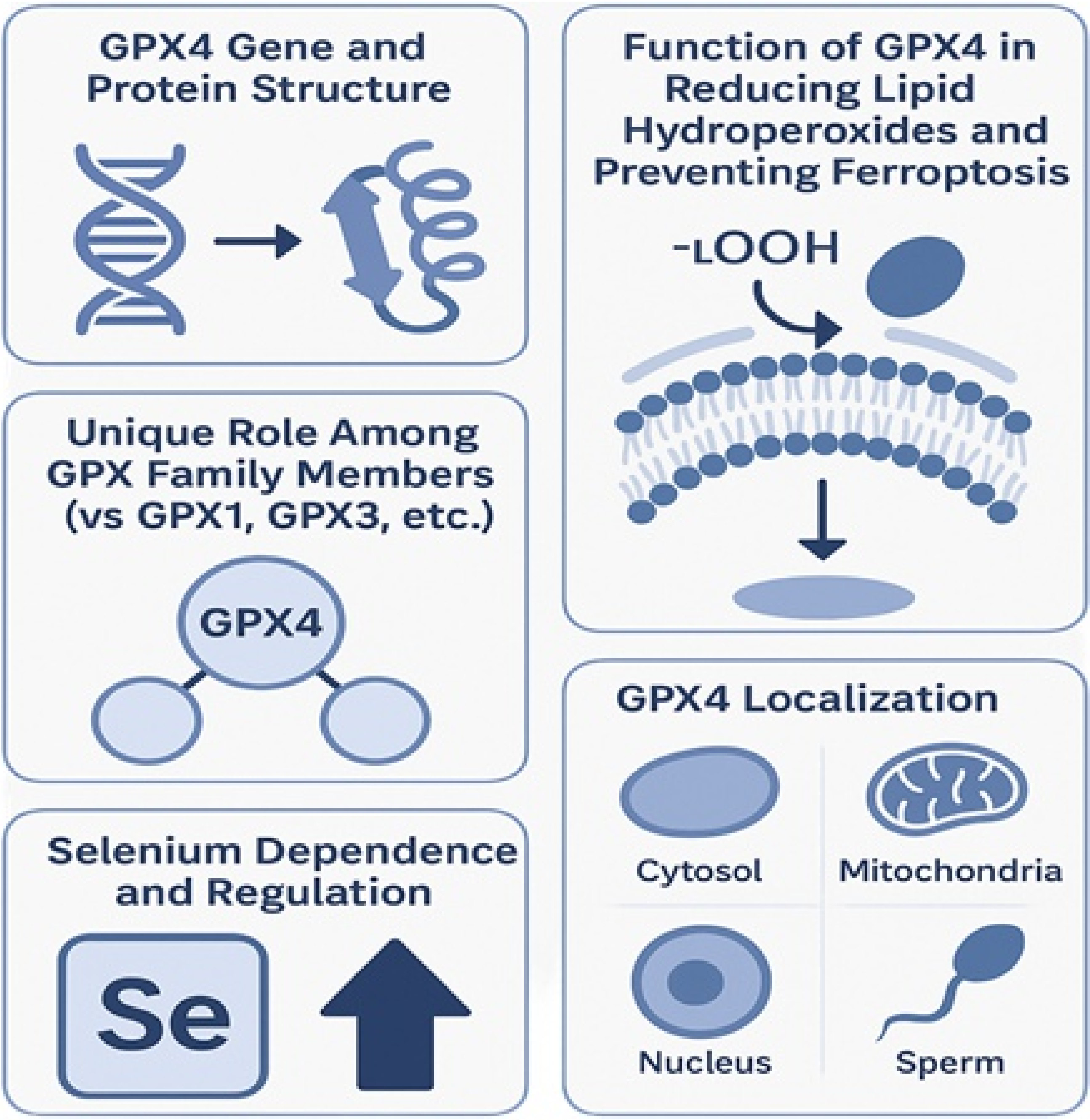


**Figure 3: GPX4: Structure and Function**

This infographic illustrates the gene and protein structure of GPX4, its role in reducing lipid hydroperoxides and preventing ferroptosis, its unique function compared to other GPX isoenzymes, its subcellular localization (cytosol, mitochondria, nucleus, sperm), and its selenium dependency and regulation [6].

Glutathione peroxidase 4 (GPX4) plays a vital role in cellular defense by reducing lipid hydroperoxides-including those embedded within biological membranes-into non-toxic lipid alcohols, using glutathione (GSH) as a cofactor [35]. This catalytic activity makes GPX4 essential for preventing ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death. Unlike other members of the GPX family, such as GPX1 and GPX3, which primarily act on hydrogen peroxide and small-molecule hydroperoxides, GPX4 uniquely targets complex membrane-bound lipid peroxides [36]. Structurally, GPX4 exists as a monomer without a tetramerization loop, enabling it to access and detoxify phospholipid hydroperoxides within membranes. Its physiological relevance is underscored by its necessity in mammalian development-GPX4 knockout leads to embryonic lethality, whereas deletions of other GPX isoforms are survivable [37].

GPX4 also plays specialized roles beyond antioxidant defense. It is critical for sperm maturation, where it contributes structurally to chromatin compaction in spermatozoa [38]. GPX4 exists in three isoforms: cytosolic (cGPX4), mitochondrial (mGPX4), and nuclear (nGPX4), each serving distinct functions in cellular antioxidant defense, mitochondrial protection, and chromatin integrity, respectively [6]. Tissue expression is highest in the testis, though it is broadly present throughout the body [39].

Crucially, GPX4 activity depends on the presence of selenocysteine at its active site, making selenium an essential micronutrient for its function. Dietary selenium deficiency impairs GPX4 activity and increases vulnerability to oxidative stress and ferroptosis [40]. Regulation of GPX4 occurs at multiple levels-including transcriptional control, incorporation of selenocysteine during translation, and post-translational mechanisms. Selenoprotein P (SeP) supports this system by maintaining cellular selenium homeostasis, particularly under conditions of stress or disease [41]. GPX4 is indispensable for lipid peroxide detoxification, ferroptosis suppression, reproductive health, and overall cellular resilience.

**Table 1 : Role of GPX4 in Thyroid Health**

| Aspect | Details | Supporting Studies / Notes |
|---|---|---|
| Expression of GPX4 in thyroid tissue | GPX4 is highly expressed in thyroid follicular cells (thyrocytes); localized in cytosol and mitochondria. | [42] |
| Antioxidant defense in thyroid follicular cells | Neutralizes hydrogen peroxide ($H_2O_2$) and lipid hydroperoxides generated during thyroid hormone synthesis ($T_3$/$T_4$). | Selenium-dependent GPXs reduce oxidative stress from TPO-mediated iodination; GPX4 uniquely protects membrane lipids [43] |
| Protection against lipid peroxidation in thyrocytes | GPX4 reduces phospholipid hydroperoxides, preventing ferroptosis and maintaining cellular integrity of thyrocytes. | [44] |
| GPX4 and selenium interaction in hormone regulation | GPX4 is a selenoprotein; its synthesis is selenium-dependent. Adequate selenium ensures proper antioxidant function and supports thyroid hormone biosynthesis. | [34] |
| GPX4 expression in hypothyroid vs euthyroid states | Animal studies show reduced GPX4 mRNA and activity in hypothyroid rats; human studies show altered selenium/GPX4 levels in thyroid dysfunction (e.g., Hashimoto). | [45] |

GPX4 and Oxidative Stress in Subclinical Hypothyroidism (SCH)

Glutathione Peroxidase 4 (GPX4) plays a pivotal role in regulating redox balance, and its dysfunction has been increasingly associated with the pathogenesis of SCH [46]. Emerging evidence suggests that reduced GPX4 activity may contribute to the progression of SCH by failing to adequately neutralize lipid hydroperoxides and other reactive oxygen species (ROS) within thyroid tissues [47]. This redox imbalance can lead to oxidative damage of thyrocytes, impairing their functional capacity even in the presence of normal circulating thyroid hormone levels [15].

GPX4's unique role in preventing lipid peroxidation offers a critical antioxidant defense mechanism that may help delay or prevent early thyroid dysfunction [48]. Given the oxidative vulnerability of the thyroid gland-largely due to hydrogen peroxide (H?O?) production during hormone synthesis-the protective actions of GPX4 become even more essential in maintaining cellular integrity under subclinical stress conditions [49].

Interestingly, there is a hypothetical but biologically plausible role for GPX4 in modulating thyroid-stimulating hormone (TSH) receptor signaling [50]. Oxidative stress has been shown to alter membrane fluidity and receptor sensitivity, and since GPX4 protects against lipid peroxidation, it may indirectly preserve TSH receptor function and downstream signaling pathways [51]. This suggests a potential mechanistic link between antioxidant defense and hormone signaling regulation in the thyroid [51].

Furthermore, selenium-a key cofactor required for GPX4 synthesis and activity-is often found to be reduced in SCH patients. Selenium deficiency can further impair GPX4 function, exacerbating oxidative stress and potentially accelerating thyroid dysfunction [52]. This dual impact highlights a feedback loop where decreased selenium availability leads to lower GPX4 activity, contributing to worsening oxidative damage and thyroid impairment [53].

Ferroptosis emerged as one of the fast-growing fields of research, i.e., an iron-dependent, regulated form of programmed cell death triggered by lipid peroxidation that is directly countermanded by GPX4. In the context of subclinical hypothyroidism (SCH), a reduced GPX4 activity may theoretically incline the cellular redox balance in such a way that it may threaten ferroptotic death of the thyroid follicular cells and, in this way, provide a new path to a subclinical destruction of the thyroid [54]. Despite the need of further investigation, the relationship between ferroptosis, GPX4 deficiency and SCH adds a new dimension to the modern understating of thyroid redox biology [55].

Relevance of Ferroptosis in Thyroid Dysfunction

Ferroptosis is a form of cell death, produced by iron-dependent oxidation of lipids that is programmed. In the thyroid gland, the key regulator of enzyme activity is glutathione peroxidase 4 (GPX4), the reduced expression or activity of which may result under the conditions of selenium deficiency, oxidative stress, or the direct GPX4 inhibition [56]. This leads to loss of the GPX4 protection hence ferroptotic cell death of the thyrocytes which not only leads to tissue loss but also to thyroid dysfunction [42]. Even though majority of the research on GPX4 and ferroptosis has focused on oncology or animal models, the entitled mechanism is relevant: such malfunctioning of GPX4 within the thyrocytes in the case of systemic chronic hypothyroidism (SCH) could induce ferroptotic cell death, which subsequently decreases the production of thyroid hormones, and the latter increases thyroid dysfunction [4].

## FUTURE DIRECTION

Despite the growing number of research findings that point to the importance of the oxidative stress and selenoproteins, most prominently glutathione peroxidase 4 (GPX4), in thyroid physiology, there exists a very large gap in the literature with regards to actual clinical connections between GPX4 and subclinical hypothyroidism (SCH). The information at hand is largely extrapolated on indirect sources of data like oxidative-stress markers, serum concentrations of selenium and simulations with animals, which makes any solid determination of how GPX4 can be involved in the early phases of thyroid malfunction somewhat hypothetical. This knowledge gap can only be bridged by cross-sectional studies that cross-sectionally assay GPX4 enzyme activity, selenium status and various oxidative-damage markers at the same time, and by longitudinal studies of both thyroid-hormone patterns and thyroid-stimulating hormone (TSH) levels of patients who are newly diagnosed with SCH. This can be clarified by such studies as to whether or not baseline GPX4 status is a predictive element of disease progress or remission that can inform on the devising of early-intervention policies.

The introduction of GPX4-based analysis into personalized treatment models has the possibility to alter the clinical practise of SCH by allowing selective prescribing of antioxidative or selenium dietary supplements to individuals who have real-world GPX4 deficiency or pseudopseudo chromes. The present evidence suggests that the direct control on GPX4 activity in the follicular cells of the thyroid by the dietary factors and micronutrients other than selenium is direct, but under-researched. The possibility to determine adjunctive medicines that cope with redox homeostasis and stabilize the thyroid activity through systematic nutritional studies designed to clarify the GPX4 modulation exists.

A multitier approach, comprising studies pertaining to in vitro experiments performed on cultured human thyrocytes can be recommended in the future studies with the aim to understand protective mechanisms proposed by GPX4 against oxidative stress and how it interacts with the TSH receptor signaling system. The role of GPX4 expression in association with thyroid dysfunction will further be elucidated by using complementary in vivo studies in animal models recapping early thyroid failure in animal models or selenium depletion studies over time. Finally, properly designed clinical trials that use GPX4-specific indicators in addition to usual thyroid biochemical tests will be essential to transfer the knowledge to patients. The other research gaps should be addressed to achieve the maximum of the therapeutic and diagnostic value of GPX4 in relation to subclinical hypothyroidism, i.e., prevent the development of overt hypothyroidism and have a better prognosis of the long-term patient treatment.

**CONCLUSION**

Subclinical hypothyroidism (SCH) is a conceptually dynamic and clinical relevant state that goes beyond the threshold of pure hormonal imissue. Traditionally, it has been a convention to describe such a condition as a mild or early form of thyroid dysfunction, but now Oxford Dictionary of the Period only categorises it as a thyroid disorder. Glutathione Peroxidase 4 (GPX4) emerges as a key antioxidant enzyme under these redox-sensitive conditions that may help define the difference between the viability of thyroid cells and their oxidative damage.

Having considered the thyroid imbalance, GPX4 is an essential part of the redox regulation of healthy cells and thyroid normalcy in particular. Its primary role is to decrease the amount of lipid peroxides, thus providing protection of cells against ferroptotic pathways. This makes it possible to consider GPX4 also, as an active controller of thyroid activity, especially at the beginning of the dysfunction, when there is the presence of subclinical hypothyroidism (SCH). There is a developing understanding that low GPX4 is found in SCH when it is associated with increased oxidative stress, and that this relationship is further supported by the catalase-sensitive GPX4 reduction at physiological selenium levels. The results also point at the importance of nutrition and regulatory procedures in sustaining the redox balance in the thyroid.

The presumed involvement of the glutathione peroxidase 4 ( GP4) in adjusting the sensitivity of the TSH receptor and signaling represents a fresh dimension of how antioxidant systems blend into the endocrine signaling pathways. Despite the lack of direct clinical evidence, initial studies and mechanistic knowledge make it a strong argument that the GPX4 should be further investigated as a biomarker and a target of treatment in SCH.

All these findings combined show that GPX4 is one of the key molecules bridging the gap between oxidative stress and thyroid dysfunction in patients with subclinical hypothyroidism. These observations indicate that additional studies of GPX4 could help diagnose patients at an earlier stage, stratify risks, and guide preventative medicine to people who are on their way to developing full-blown hypothyroidism. Further research needs should thus strive to identify the characteristic functional effect of GPX4 in the thyroid physiology, define its regulatory role under the influence of micronutrients, including selenium, and assess its possible implementation in individualized treatment procedures. There is an increasing need to have a more sophisticated understanding of the redox-thyroid axis that may eventually towards a better treatment of subclinical thyroid diseases.

**CONFLLICT OF INTEREST**

None

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