

Targeting Oxidative Stress in Thyroid Disorder: Therapeutic Potential of N-Acetylcysteine

Aneesh Parmar^{1*}, Abhishek Kumar¹, Amar Deep Ankalgi¹, Ankit Sharma¹, Aditi Kaushik¹, Mahendra Singh Ashawat²

¹Department of Pharmaceutical Analysis, Laureate Institute of Pharmacy, Kangra, Himachal Pradesh, India

²Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra, Himachal Pradesh, India

Corresponding Author Email: parmaraneesh5@gmail.com

E-mail Id's of Co-authors: abhi12002g@gmail.com, amarchemlogin@gmail.com, ankitsharma0506@gmail.com, msaresearch@gmail.com

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Abstract: Thyroid disorders, including hyperthyroidism, Graves' disease, Graves' ophthalmopathy, Hashimoto's thyroiditis, and hypothyroidism, are among the most prevalent endocrine diseases worldwide and are associated with substantial metabolic, cardiovascular, and immunological complications. Increasing evidence indicates that oxidative stress plays a pivotal role in their pathogenesis by promoting mitochondrial dysfunction, chronic inflammation, immune dysregulation, and cellular injury. Although conventional therapies effectively restore thyroid hormone homeostasis and relieve clinical symptoms, they do not directly address the underlying oxidative mechanisms involved in disease progression. Consequently, antioxidant-based adjunctive therapies have attracted growing research interest. N-Acetylcysteine (NAC), a well-established antioxidant and precursor of glutathione, exhibits multiple biological activities beyond free radical scavenging, including restoration of intracellular glutathione, activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, inhibition of nuclear factor-kappa B (NF- κ B)-mediated inflammation, preservation of mitochondrial function, and modulation of immune responses. This mini-review summarizes current evidence regarding the role of oxidative stress in thyroid physiology and thyroid disorders and discusses the molecular mechanisms through which NAC may confer therapeutic benefits. Preclinical studies consistently demonstrate that NAC attenuates oxidative damage, restores antioxidant defenses, and protects against hyperthyroidism-induced tissue injury, particularly in experimental cardiomyopathy. However, clinical evidence supporting its use in thyroid disorders remains limited, especially in autoimmune thyroid diseases. Future well-designed clinical trials are required to establish the efficacy, optimal dosage, treatment duration, and long-term safety of NAC. Overall, NAC represents a promising adjunctive strategy for targeting oxidative stress in thyroid disorders and warrants further translational investigation.

Keywords: N-acetylcysteine; thyroid disorders; oxidative stress; hyperthyroidism; Graves' disease; antioxidants.

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Introduction

Among the most common types of endocrine disorders, thyroid diseases are known to occur in people of all ages and contribute to significant morbidity both from a medical and socio-economic point of view. Thyroid diseases include such conditions as hyperthyroidism, hypothyroidism, Graves' disease, Hashimoto's thyroiditis, thyroid eye disease, and thyroid cancer. They lead to thyroid hormone homeostasis disruption, affect the function of the cardiovascular system, metabolism, nervous system, and immune function. As a result, there is a notable impact on the quality of patients' lives. The causes of these conditions may differ; however, recent studies confirm the role of oxidative stress in their development and progression [1-3].

Current treatments mostly concentrate on restoration of euthyroidism and relief of symptoms. In the case of hyperthyroidism, treatments include the use of antithyroid drugs (methimazole, carbimazole, and propylthiouracil), radioiodine ablation, and thyroidectomy [4-6]. In cases of autoimmune thyroid diseases, it is possible to control hormones' imbalance and address manifestations specific to particular disease, including immunotherapy and supportive care for Graves' ophthalmopathy [7,8]. Unfortunately, these treatment methods do not address the issue of oxidative and inflammatory processes leading to the development of the disease [9].

In addition, side effects of therapy, relapse of the disease, and permanent tissue damage are still clinically significant problems that warrant the use of supportive treatment modalities that take into account molecular aspects of thyroid pathology [6]. It is known that the thyroid gland is especially prone to the effects of oxidative damage due to its physiology, which implies the constant production of hydrogen peroxide (H_2O_2), which is required for iodine reactions performed by thyroid peroxidase [10]. Normally, the body's endogenous antioxidants (glutathione, superoxide dismutase, catalase, and glutathione peroxidase) maintain redox balance through the neutralization of excess free radicals. However, oxidative stress occurs due to excessive production of ROS or failure of antioxidant systems. Chronic oxidative stress causes lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, inflammatory cytokines production, immune disorders, which leads to the development and progression of hyperthyroidism, Graves' disease, Hashimoto's thyroiditis, thyroid eye disease, and their complications [11].

Among the various possible antioxidants, the use of N-acetylcysteine (NAC) has shown great promise due to the already established pharmacology and safety profile of the drug [12]. NAC is an N-acetyl derivative of L-cysteine and acts as a substrate for the production of glutathione, an important antioxidant produced within the cells. In addition to replenishing the stores of glutathione, NAC has scavenging activity against free radicals, inhibits pro-inflammatory pathways, maintains mitochondrial integrity, and affects redox-sensitive responses of the cells. Though NAC has been approved for treating acetaminophen intoxication and mucus clearance in chronic respiratory conditions, recent research on NAC in laboratory and clinical settings has indicated its possible uses in various oxidative stress-related diseases such as those affecting the central nervous system, cardiovascular system, kidneys, lungs, and the endocrine glands. However, most importantly, there is evidence that the modulation of oxidative stress through the use of NAC can

help in avoiding the damage to thyroid tissue and the complications of excess thyroid hormone action, which makes NAC a good candidate for use in thyroid disease [13–18].

This review provides information concerning the involvement of oxidative stress in thyroid pathologies and assesses the possibility of using NAC as a therapeutic agent with redox-modulating action. Special attention will be paid to the molecular pathways of the association between oxidative stress and thyroid dysfunctions, evidence in favour of NAC treatment from experiments and clinics, limitations of existing research, and future prospects in this field.

Oxidative Stress in Thyroid Physiology and Pathophysiology

Oxidative Stress in Normal Thyroid Physiology

One of the unique features of the thyroid gland is the presence of continuous production of reactive oxygen species (ROS) within it as an integral part of normal physiological processes. As opposed to other tissues, where an excessive generation of ROS is usually related to cell damage, the thyroid gland uses oxidative reactions under physiological control as the basis for thyroid hormones synthesis. The synthesis of these hormones starts with transport of iodide ions to the follicular cells of the thyroid gland using sodium/iodide symporter followed by the oxidation by thyroid peroxidase (TPO) protein. The oxidation reaction needs hydrogen peroxide (H_2O_2) as an oxidant, which is mainly produced in follicular cells of the thyroid gland by dual oxidase (DUOX1 and DUOX2) enzymes at the apical membrane. Generated H_2O_2 acts as an indispensable oxidizer required for tyrosyl group iodination in thyroglobulin and coupling reactions, resulting in T_4 and T_3 production [14,19,20].

Despite the constant production of reactive oxygen species (ROS), there is an effective antioxidant system for maintaining redox balance in the cells of the thyroid gland. This system includes enzymatic antioxidants, such as SOD, catalase, GPx, glutathione reductase, and peroxiredoxins, and non-enzymatic antioxidants like GSH, vitamins C and E, and thioredoxin. The above-listed mechanisms of antioxidant protection allow one to scavenge ROS, which minimizes oxidative damage and maintains cell integrity., shown in Figure 1. Out of the mentioned mechanisms, the glutathione system has a key importance in the processes of detoxification of oxidants and redox balance maintenance. Under physiologic conditions, the balanced interaction of ROS production and antioxidant protection allows for the normal production of thyroid hormones without damaging the follicular cells [9,21,22].

Oxidative Stress in Thyroid Pathophysiology

Oxidative stress occurs due to an imbalance of the controlled production of reactive oxygen species (ROS) and antioxidant protection against it (Figure 1). The imbalance leads to the development of an excess amount of ROS in comparison with the neutralization by endogenous antioxidant defence. Oxidative stress in thyroid disorders is caused by an increased metabolism rate, malfunction of mitochondria, inflammation and autoimmune reactions. Excess ROS lead to lipoperoxidation, protein and DNA damage, mitochondrial dysfunction and redox-sensitive signalling pathway activation. Recent research shows that oxidative stress is not just the consequence but also the factor in the development of the disorder [21,23].

In hyperthyroidism, elevated levels of thyroid hormones result in an increase in basal metabolic rate and mitochondrial oxygen consumption, which leads to excess ROS generation. This oxidative condition has been linked to increased lipid peroxidation, endogenous antioxidants depletion, and decreased total antioxidant activity. Studies in clinical settings have shown significant elevation in malondialdehyde (MDA), a marker of lipid peroxidation, along with the deficiency of antioxidants in patients who are untreated for hyperthyroidism. Reestablishment of euthyroid status after the administration of antithyroid drugs has led to partial normalization of oxidative balance; nevertheless, oxidative stress often remains, indicating that standard treatments do not fully reverse oxidative imbalance [23].

Other examples of the interplay between oxidative stress and immune dysregulation are represented by autoimmune conditions that involve the thyroid gland. For instance, oxidative stress in Graves' disease causes increased inflammation, cytokines synthesis, and autoimmune response targeting thyroid tissues. In addition, oxidative stress plays a part in developing Graves' ophthalmopathy through its effect on orbital fibroblasts proliferation, extracellular matrix remoulding, and chronic inflammation. In Hashimoto's thyroiditis, ongoing oxidative damage increases antigen presentation, inflammatory cells recruitment, and follicular destruction by autoimmune response [24–26].

From these findings, it can be concluded that oxidative stress acts as a common pathogenic link in the interaction of thyrotoxicosis, thyroiditis, and other thyroid diseases with chronic inflammation and impaired immune system function due to the imbalance of thyroid hormones. The increasing role attributed to oxidative stress in the development of these conditions has led to the exploration of antioxidant treatment methods, which would not only normalize the levels of thyroid hormones but also restore cellular redox balance, maintain normal mitochondrial function, and minimize inflammatory processes. Thus, oxidative stress management has become a promising additional strategy for the treatment of thyroid diseases [1,27].

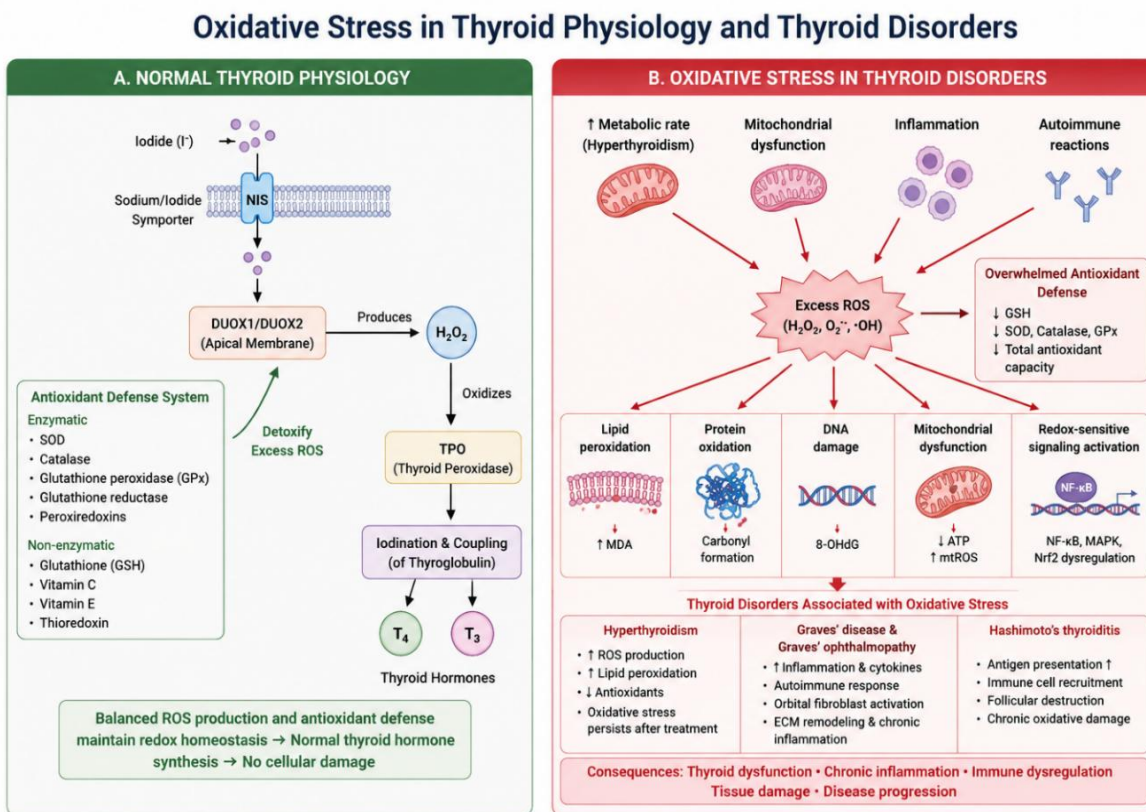


Figure 1: Physiological and pathological roles of oxidative stress in thyroid function and thyroid disorders

Molecular basis for N-Acetylcysteine Therapy

N-acetylcysteine (NAC) is a chemical analogue of the amino acid L-cysteine, being the N-acetyl derivative of the latter. It has been utilized as an effective medicine in clinical practice for over half a century because of excellent safety and wide therapeutic action. The drug was initially utilized as a mucolytic substance and soon became the preferred treatment for acetaminophen poisoning [12,28]. However, N-acetylcysteine

attracted increasing interest as a versatile antioxidant with promising application for many oxidative stress-induced diseases. Biological action of NAC goes beyond the well-known medical uses of the drug and is mainly determined by the ability of NAC to maintain glutathione balance inside cells, control redox status, support mitochondrial functioning, reduce inflammation and affect immunity (Figure 2). All these effects can serve as a good foundation for further research into the application of NAC in the treatment of thyroid diseases complicated by oxidative stress and inflammation [29,30].

NAC Chemistry and Glutathione Synthesis

NAC is chemically an acetylated form of L-cysteine having an unmodified sulfhydryl (-SH) group responsible for several biological actions. After oral or intravenous administration, NAC is quickly converted to cysteine, which is the precursor to reduced glutathione (GSH), the body's primary antioxidant. GSH is involved in the detoxification of hydrogen peroxide and lipid hydroperoxides by glutathione peroxidase while at the same time ensuring redox balance within the cell. In the presence of oxidative stress, the intracellular pools of glutathione become depleted. The use of NAC helps restore the levels of GSH in the cells. This process is especially important in tissues that have a high level of oxidative metabolism such as the thyroid gland, which requires continual production of hydrogen peroxide for the production of thyroid hormones [31,32].

Activation of the Nrf2 Antioxidant Pathway

Another important cytoprotective mechanism of N-Acetylcysteine is the ability to regulate the Nrf2 signaling pathway [33]. Physiologically, Nrf2 exists in the cytoplasm in association with Kelch-like ECH-associated protein 1 (Keap1). As a result, Nrf2 undergoes ubiquitination and proteasomal degradation. In oxidative stress, Nrf2 dissociates from Keap1, and migrates into the nucleus, and then associates with the antioxidant response elements (AREs), resulting in the transcription of a number of cytoprotective genes. These genes include heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), glutamate-cysteine ligase (GCL), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase. Studies have shown that NAC protects cells from oxidative damage by regulating Nrf2 and keeping glutathione-mediated redox signaling intact [34,35].

Inhibition of NF- κ B Signaling and Anti-inflammatory Effects

Oxidative stress and inflammation have a significant association in terms of the redox-dependent signaling pathway, wherein nuclear factor-kappa B (NF- κ B) is a key regulator of the inflammatory response. An elevated amount of ROS stimulates NF- κ B and leads to upregulation of pro-inflammatory cytokines, chemokines, cell adhesion molecules, and inflammatory enzymes such as cyclooxygenase-2 and inducible nitric oxide synthase. NAC inhibits the process of ROS-mediated NF- κ B stimulation, resulting in a decreased level of transcription of TNF- α , IL-1 β , IL-6, and other inflammatory mediators. Thus, NAC disrupts the self-sustained loop of oxidative stress-mediated increase in inflammation and the latter's contribution to the elevation of ROS production. This mechanism might prove valuable in autoimmune disorders of the thyroid gland, in which chronic inflammation contributes to tissue damage [32,36-38].

Mitochondrial Protection

Mitochondria serve as important sources and targets for ROS under oxidative stress. Increased ROS cause mitochondrial membrane dysfunction, decrease ATP synthesis, cause mitochondrial DNA damage, and initiate cell death. NAC is shown to be very effective at protecting mitochondria by regaining their intracellular glutathione levels, lowering mitochondrial ROS formation, preventing loss of mitochondrial membrane potential, and improving oxidative phosphorylation. There are many experimental evidences suggesting that NAC prevents mitochondrial dysfunction, inhibition of apoptosis, and improves cell survival in the presence of oxidative stress. Since the dysfunction of mitochondria is involved in the

development of oxidative stress caused by thyroid hormones, maintenance of mitochondrial function provides another way of its action [29,39–42].

Molecular Mechanisms of N-Acetylcysteine (NAC) in Thyroid Disorders

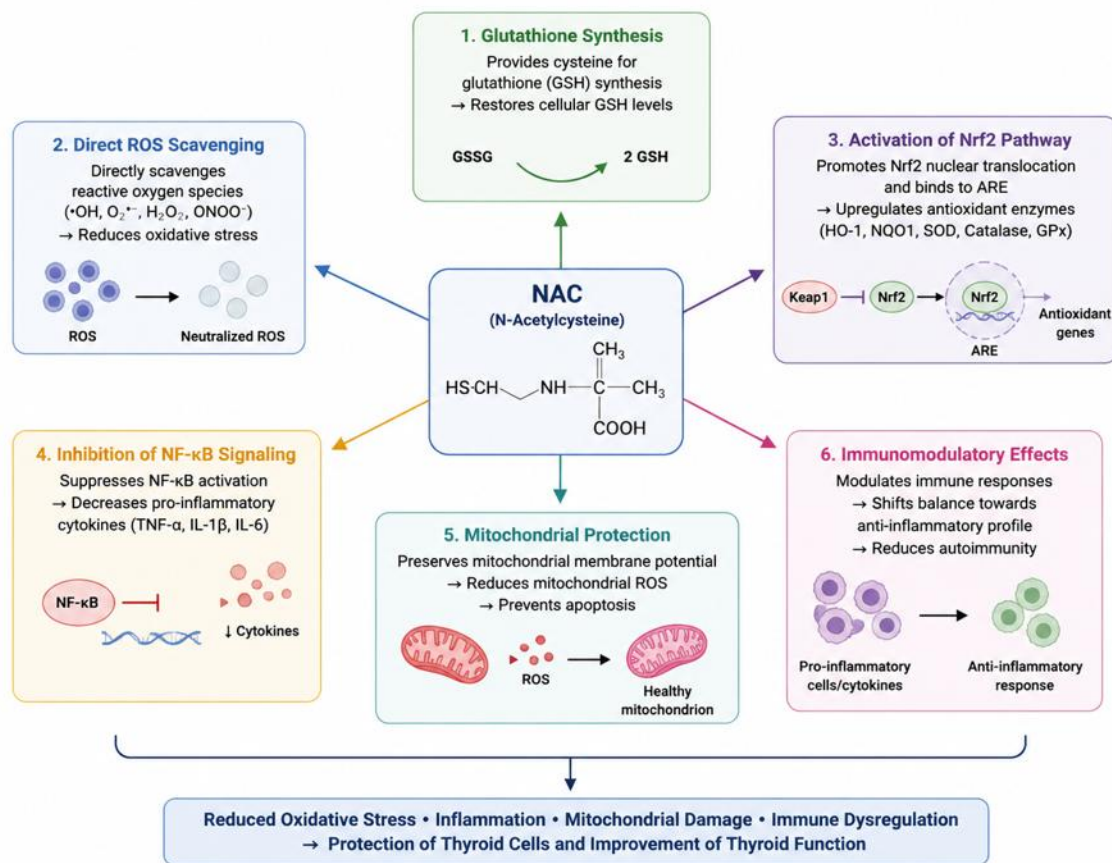


Figure 2: Molecular mechanisms underlying the therapeutic actions of N-acetylcysteine (NAC) in thyroid disorders.

Immunomodulatory Properties

Apart from being antioxidant and anti-inflammatory, NAC also shows some significant immunomodulatory actions. Regulation of redox equilibrium within cells by NAC affects the activation, proliferation, and differentiation of immune cells like T lymphocytes, macrophages, dendritic cells, and neutrophils. By restoring the balance of glutathione, NAC prevents excessive immune system activation and cytokine synthesis without affecting the normal functions of the immune system. Some experimental studies also show that NAC affects the polarization of macrophages, inflammasome activation, and oxidative stress-induced immune dysfunction. The above-mentioned immunomodulating effects of NAC may be quite useful for treating autoimmune thyroid diseases like Graves' disease and Hashimoto's thyroiditis, where oxidative stress and immune activation cause the destruction of thyroid tissue [43].

Indeed, the diverse therapeutic effects of NAC are not limited to antioxidant treatment only. Through the process of restoring the glutathione balance, NAC can directly scavenge reactive oxygen species, activate Nrf2 pathway that regulates the production of antioxidants, inhibit NF-κB pathway which is responsible for inflammatory responses, maintain mitochondrial function, and modulate immune response. Thus, by

targeting a number of different but related pathways which are responsible for the development of disease associated with oxidative stress, NAC offers a strong biological background for further testing its therapeutic potential in thyroid disorders [12,32,43].

Experimental and Emerging Evidence for N-Acetylcysteine in Thyroid Disorders

Preclinical Evidence Supporting NAC Therapy

N-acetylcysteine (NAC) therapy for thyroid conditions is based on preclinical studies showing the effect of NAC to decrease oxidative stress, maintain the integrity of mitochondria, and mitigate inflammatory processes. While the number of thyroid-related experimental studies is not high, there is abundant evidence from *In Vitro* and animal experiments about the role of NAC in restoring redox balance and protecting cells from oxidative damage. The mechanisms of NAC effect give enough rationale to explore its application as a complementary therapy in patients with thyroid disorders, where oxidative stress, mitochondria dysfunction, and inflammation play an important role [29,32].

Table 1: Experimental studies evaluating NAC in thyroid disorders.

Reference	Model	NAC Regimen	Findings	Relevance
[29]	<i>In Vitro</i> thyroid cells exposed to inflammatory/oxidative stress	NAC used experimentally	NAC protected thyroid cells from oxidative stress and inflammatory injury; ROS are crucial in thyroid hormonogenesis and OS is toxic to thyrocytes	Strong mechanistic support for thyroid-cell antioxidant protection
[46]	Rat model of hyperthyroidism	NAC 50 mg/kg orally, daily for 3 weeks	NAC reduced MDA and nitric oxide, increased glutathione, SOD, and catalase, and prevented apoptosis/DNA damage and histopathological injury	Best experimental evidence for NAC in hyperthyroidism-related oxidative injury.
[47]	Randomized clinical trial in myocardial infarction patients with NTIS	NAC 1,200 mg IV every 12 h for 48 h	NAC attenuated the fall in T3 compared with placebo	Relevant to thyroid hormone regulation under systemic stress, though not a thyroid disorder model.

In Vitro Studies

In cell-based research, it has been found that NAC helps to decrease ROS production inside cells while maintaining the balance of glutathione (GSH) levels by delivering cysteine, which is the limiting amino acid for the formation of GSH. The replenishment of GSH inside the cell increases the antioxidant level while preventing oxidative damage to lipids, proteins, and DNA molecules. Additionally, NAC decreases the pro-inflammatory response via the suppression of the activation of nuclear factor-kappa B (NF- κ B), causing a decrease in the levels of TNF- α , IL-1 β , and IL-6 cytokines [14,44].

Animal Models

More evidence on the antioxidant effects of NAC is provided by animal studies on the condition of hyperthyroidism. Experimentally induced hyperthyroidism was found to be always connected with increased lipid peroxidation, decreased activity of natural antioxidants, mitochondrial dysfunction, and tissue damage. Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities were substantially normalized due to NAC treatment, whereas malondialdehyde (MDA) levels were significantly decreased. The latter compound serves as a marker of lipid peroxidation. In addition, the mitochondrial dysfunction was attenuated, apoptosis was prevented, and oxidative damage of tissues was decreased [45,46].

Evidence in Hyperthyroidism

The overproduction of thyroid hormones is observed in hyperthyroidism, which causes increased metabolism, mitochondrial oxygen utilization, and greater synthesis of reactive oxygen species (ROS). A growing number of scientific reports state that oxidative stress is one of the most common factors causing tissue injury during hyperthyroidism and can be prolonged even after normalization of euthyroidism, thus, indicating that the existing therapy cannot compensate for this problem. Clinical data revealed the changes in the parameters of oxidative stress in the patients who did not undergo treatment for hyperthyroidism. The increased level of serum malondialdehyde (MDA), which is considered a lipid peroxidation marker, is characterized by low activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and lower concentrations of reduced glutathione (GSH). In addition, the total antioxidant capacity (TAC) of the body is significantly decreased.

Antithyroid drug treatment with medications like carbimazole and methimazole has been proven effective in reducing oxidative stress by minimizing serum levels of thyroid hormones. There is significant reduction in MDA along with recovery of antioxidant enzymes and TAC in addition to the use of antioxidant treatment. Yet there are several studies showing that oxidative stress persists despite euthyroidism, implying the need for a different approach for the treatment of oxidative stress. Despite lack of clinical trials on NAC in patients with hyperthyroidism, the beneficial properties of this medication make a compelling case for its use. Through its antioxidant and cytoprotective effects, it can help increase glutathione levels, decrease ROS formation, maintain mitochondrial integrity, and inhibit inflammatory mediators in patients with hyperthyroidism. The experimental results point toward the possibility of using NAC in combination with standard treatment of hyperthyroidism through the use of antithyroid medications, although further randomized clinical trials are needed to determine its clinical effect and proper dose [9].

NAC in Hyperthyroidism-induced Cardiomyopathy

Hyperthyroidism is related to severe heart alterations caused by high thyroid hormones level, such as increased heart work, increased oxygen consumption by mitochondria and excess ROS generation. Chronic oxidative stress causes disorders in calcium metabolism through activation of ROS/Ca²⁺ signaling pathway and leads to mitochondrial impairment, cardiomyocyte apoptosis, myocardial fibrosis and heart

remodelling. All this contributes greatly to the emergence of cardiomyopathy caused by hyperthyroidism [9].

The positive influence of N-acetylcysteine (NAC) on heart function during hyperthyroidism-induced cardiomyopathy in rats has been demonstrated [14]. Treatment with NAC led to reduction of oxidative stress in myocardium, normalization of antioxidant status and improved morphology and function of the heart. All this was due to inhibition of ROS/Ca²⁺ signaling pathway that decreased calcium overload in cells, preserved integrity of mitochondria and prevented oxidative damage. In addition, NAC inhibited apoptosis of cardiomyocytes and myocardial fibrosis that indicated its capability to limit morphological and functional changes of the heart under the influence of excess thyroid hormones.

The results from these experiments show that NAC has several cardioprotective roles due to its ability to restore redox balance, maintain calcium balance, maintain mitochondrial function, and inhibit oxidative stress-induced cell death. While the available scientific data has been obtained from animal studies alone, the constant beneficial effects demonstrated in animal experiments make it possible to predict the usefulness of NAC as an auxiliary treatment for reducing complications of hyperthyroidism on the cardiovascular system. Nonetheless, further research in the form of well-controlled clinical experiments is needed to confirm this prediction.

Emerging Evidence in Autoimmune Thyroid Diseases

Autoimmune thyroid disorders (AITD) such as Graves' disease (GD), Graves' ophthalmopathy (GO), and Hashimoto's thyroiditis (HT) are characterized by chronic inflammation, immune dysfunction, and ongoing oxidative stress. Overproduction of ROS leads to enhanced inflammatory signaling, increased production of cytokines, and damage of tissues, and hence oxidative stress plays an important role in the treatment of these conditions. In Graves' disease, oxidative stress increases the activity of redox-sensitive signaling pathways like NF- κ B that ultimately lead to proinflammatory cytokines production. While there are no existing studies concerning NAC in Graves' disease, the known effects of NAC on enhancing the level of glutathione, inhibiting oxidative stress, and blocking the inflammatory pathway make NAC a promising candidate for adjunct therapy in GD. The mechanism of antioxidants has shown positive results in several other immune-mediated diseases and may play an important role in thyroid autoimmune conditions [21,48].

Graves' ophthalmopathy, one of the most common extrathyroidal manifestations of Graves' disease, is defined by activation of fibroblasts in orbit, excessive accumulation of extracellular matrix, fat deposition and inflammation. One of the major players in orbital tissue remodeling is oxidative stress, which stimulates proliferation of fibroblasts and formation of inflammatory mediators. Experiments show that reduction of oxidative stress may decrease activation of fibroblasts and tissue remodeling; thus, application of NAC may help to control the disease using its antioxidant and anti-inflammatory effects. Nevertheless, direct experiments and clinical studies on the effect of NAC in this condition are not available at the moment [48,49].

Hashimoto's thyroiditis is a chronic autoimmune disease which is characterized by continuous inflammation, oxidative stress, increased antigen presentation and degeneration of thyroid follicles. The recent researches have revealed the role of impaired antioxidant status and redox regulation in the development of this disease; oxidative stress can become an interesting therapeutic target due to that. Though there is no clinical study which would test the effect of NAC in Hashimoto's thyroiditis, the possible restoration of glutathione homeostasis and ROS production may be beneficial for the therapy [26,50].

Critical Appraisal and Future Research Needs

Currently available data clearly show that N-acetylcysteine (NAC) has great medicinal prospects for thyroid diseases due to its antioxidant, anti-inflammatory, and cytoprotective effects. Indeed, all preclinical research clearly shows that NAC normalizes redox state, maintains mitochondrial function, reduces inflammation and oxidative damage to tissues. All these facts make a perfect basis for using NAC for the treatment of thyroid diseases including hyperthyroidism and its complications. However, clinical implementation of the findings of preclinical research is limited. The clinical information is mostly indirect and mainly relates to the biomarkers of oxidative stress or antioxidants supplementation, not NAC in particular. Moreover, clinical studies feature small sample sizes, heterogeneous design, various treatment protocols, and lack of long-term follow-ups that prevent developing the standard treatment protocol. There is very limited clinical information regarding the use of NAC for the treatment of Graves' disease, Graves' ophthalmopathy, and Hashimoto's thyroiditis [12,15].

Differences between experimental models and the heterogeneous clinical presentation of thyroid disorders may partly explain the limited translation of promising preclinical findings into clinical practice. Future research must focus on conducting randomized controlled trials to investigate the effectiveness, appropriate dose, duration of therapy, and safety of NAC in thyroid disorders. In addition, studies that explore the use of NAC along with standard antithyroid agents, in conjunction with patient selection based on biomarkers and new formulations with increased bioavailability, could help bring this drug to the clinical setting. It is crucial to fill these research gaps for understanding the therapeutic utility of NAC in thyroid disorders.

Challenges and Future Perspectives

Despite the therapeutic promise that can be drawn from NAC in the treatment of thyroid disorders, there are a number of issues that restrict its use in clinical practice. Firstly, much of the available information is based on *In Vitro* and animal data with very few studies involving clinical trials conducted specifically on thyroid disorders. Moreover, most clinical studies have been focused on evaluation of oxidative stress parameters or antioxidants administration without specifically addressing the efficacy of NAC. Another issue that deserves attention is the absence of validated oxidative stress biomarkers to monitor and predict the effect of the therapy. Despite the fact that biomarkers such as malondialdehyde (MDA), reduced glutathione (GSH), or antioxidant enzyme activity are often used in studies, their application in clinical practice still requires validation. It is necessary to note that the poor oral bioavailability of NAC, which is determined by significant first-pass effect, should also be taken into consideration [32].

Future studies need to conduct carefully designed randomized controlled trials in order to study the effectiveness, dose regimen, course of therapy, and safety of NAC in hyperthyroidism, Graves' disease, Graves' orbitopathy, and Hashimoto's thyroiditis. The investigation of NAC as an additional treatment option to conventional antithyroid medications, such as methimazole and carbimazole, will help to reveal whether the combined treatment leads to better control of the oxidative stress and progression of the disorder in comparison with the conventional one. Further advancements in pharmaceuticals will include liposomal preparation, nanocarrier delivery systems, and N-acetylcysteine amide (NACA). In general, the accumulating evidence regarding oxidative stress role in thyroid diseases pathogenesis is a basis for the investigation of NAC. Despite the existing promising results, further translational and clinical researches are necessary to implement the treatment.

Conclusion

Recently, the role of oxidative stress in thyroid diseases has been elucidated through its impact on mitochondrial damage, chronic inflammatory processes, immune system dysfunction, and cell damage. Traditional treatment regimens can effectively correct the balance of thyroid hormones and alleviate the symptoms; however, they fail to target the oxidative processes that are involved in the disease development. Therefore, the modulation of oxidative stress has become an increasingly popular approach in addition to traditional therapy.

The use of N-Acetylcysteine (NAC) is widely recognized due to its antioxidant properties and high safety profile. In addition to the ability of NAC to increase the glutathione concentration, its biological effects are multifunctional. It is capable of removing reactive oxygen species, activation of the Nrf2 pathway, inhibition of inflammation through the inhibition of the NF- κ B pathway, protection of mitochondria, and immune system modulation. The effectiveness of NAC was repeatedly proven by experimental studies; it has been demonstrated in the case of hyperthyroidism and hyperthyroidism-induced cardiomyopathy. There is little data regarding the application of NAC in the case of autoimmune thyroid diseases.

In summary, there is currently satisfactory evidence, promising the use of NAC as a potential adjuvant agent in treating oxidative stress-related thyroid disorders. However, more well-designed clinical studies are required in order to assess its efficacy, dosing, administration time, and safety profile. Future studies that incorporate patient stratification using biomarkers and adjuvant therapy along with standard anti-thyroid medications will help further clarify the role of NAC in clinical practice. Further research in this field might result in the successful transition of NAC from a mere antioxidant to a clinically useful adjuvant.

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