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REVIEW ARTICLE
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THYROID PROFILE AND LIPID PEROXIDATION IN DOWN SYNDROME: A REVIEW

Dr. Gangadharan Jaikrishan*

*MBBS MD, Department of Biochemistry Azeezia Institute of Medical Science and Research, Meeyannoor P.O, Kollam 691 537 Kerala

***Corresponding Author:** Dr. Gangadharan Jaikrishan
* MBBS MD, Department of Biochemistry Azeezia Institute of Medical Science and Research, Meeyannoor P.O, Kollam 691 537 Kerala, Email: anjali96@yahoo.com

ABSTRACT
Trisomy 21 causes Down Syndrome(DS), a chromosome condition characterized by numerous systemic dysfunctions, of which oxidative stress and thyroid abnormalities are particularly evident. These interconnected disorders have a major role in early-onset neurodegeneration, metabolic impairment, and neurodevelopmental abnormalities. To summarize the current understanding of the relationship between thyroid dysfunction and oxidative stress in people with Down syndrome, this review will focus on common molecular pathways, clinical implications, diagnostic biomarkers, and new treatment approaches. Data on thyroid hormone modulation, oxidative damage biomarkers, and their interaction in DS were analysed by a thorough assessment of peer-reviewed literature. Molecular processes, diagnostic approaches, and translational limitations in clinical applicability were highlighted. Hypothyroidism, which is commonly asymptomatic and underdiagnosed, is a common feature of thyroid dysfunction in DS. At the same time, overexpression of genes like Superoxide Dismutase 1(SOD1) and Regulator of Calcineurin 1 (RCAN1) makes mitochondrial dysfunction and the buildup of reactive oxygen species (ROS) worse. Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE) are examples of lipid peroxidation products that not only indicate systemic oxidative stress but also reduce the activity of thyroid enzymes, especially thyroid peroxidase (TPO). Both oxidative damage and endocrine disruption are exacerbated by this reciprocal interplay. Treatment strategies are still dispersed, and hormonal and oxidative indicators are not sufficiently integrated into the current diagnosis. The oxidative stress and thyroid dysfunction both affect DS, which highlights the need for individualized treatment plans and integrated diagnostic methods. For precision medicine in DS, future research should give priority to multi-omics profiling, AI-enhanced biomarker analysis, and longitudinal cohort studies.

Keywords: Down syndrome, thyroid dysfunction, oxidative stress, lipid peroxidation, mitochondrial dysfunction

1. INTRODUCTION
Trisomy 21, often known as DS, is the most prevalent chromosomal condition, affecting approximately 1 in 700 live births in the US. The existence of an extra copy of chromosome 21 makes this a genetic condition that results in a variety of phenotypic traits, including congenital defects, intellectual disability, and facial deformities. Individuals with Down Syndromeare at risk for several health issues, including hematologic abnormalities, gastrointestinal abnormalities, congenital heart

disease, and endocrine diseases (Mégarbané et al., 2009). Thyroid dysfunction stands out among the endocrine disorders in DS individuals. DS people had a higher prevalence of congenital and acquired hypothyroidism than the general population. Preterm recognition and treatment of thyroid disease in DS may prove to be difficult due to its mild presentation, which will mask the baseline features of the syndrome. Thus, to avert the adverse effects on growth, metabolism, and mental development, regular screening and early treatment are needed (Colvin et al., 2017). Pathophysiology of DS is now recognized to be highly dependent on oxidative stress. Production of reactive oxygen species and the antioxidant defence system of the body is disturbed when the genes on chromosome 21, such as superoxide dismutase 1 (SOD1), are overexpressed. This disturbance in DS brings about enhanced lipid peroxidation, oxidation of proteins, and DNA damage, all of which are responsible for the accelerated aging and neurodegeneration in the disease. In DS, oxidative stress and thyroid dysfunction interact in a complicated manner and need to be studied meticulously. Since thyroid hormones influence oxidative metabolism and mitochondrial activity, they are expected to increase oxidative stress when defective function occurs. Similarly, oxidative damage can disable thyroid gland function; therefore, the two substances are in a vicious cycle that worsens the health status of DS patients (Ferrari et al., 2021).

1.2 Rationale for the Review

It is significant to extensively explore the intricate connection between thyroid dysfunction and oxidative stress in DS. Oxidative metabolism and mitochondrial function are regulated by thyroid hormones, and when dysfunction occurs, they would most likely enhance oxidative stress. Oxidative damage can also worsen thyroid gland function; therefore, the two are involved in a vicious circle that worsens the state of health among individuals with Down syndrome.

Table 1 emphasizes the role of Trisomy 21 in developing oxidative and endocrine issues, and the rationale for combined diagnostic and treatment models in Down syndrome.

Table 1. Key Pathophysiological and Clinical Concepts Linking Down Syndrome, Thyroid Dysfunction, and Oxidative Stress

Section	Core Theme	Key Features	Clinical/Pathophysiological Relevance	References
Overview of Down Syndrome	Chromosomal Abnormality (Trisomy 21)	- Affects 1 in 700 live births - Extra chromosome 21 - Phenotypic traits: intellectual disability, craniofacial features, congenital anomalies	Increased risk for multiple comorbidities, including hematologic, gastrointestinal, cardiac, and endocrine disorders	(Chow et al., 2017)
Thyroid Dysfunction in DS	Endocrine Abnormality	- High prevalence of congenital and acquired hypothyroidism - Often subclinical or mildly symptomatic - Difficult to detect due to symptom overlap with DS phenotype	Untreated dysfunction can impair growth, metabolism, and cognitive development; necessitates regular screening and early therapy	(Pepe et al., 2020).
Oxidative Stress and Lipid Peroxidation	Redox Imbalance and ROS Overload	- Overexpression of genes like SOD1 on chromosome 21 - Excess ROS leads to lipid peroxidation, DNA/protein damage - Accumulation of 4-HNE, MDA	Drives premature aging, mitochondrial dysfunction, and neurodegeneration in DS	(Bartley et al., 2012)

Interplay Between Thyroid and Oxidative Stress	Bidirectional Pathophysiology	- Hypothyroidism exacerbates ROS production via mitochondrial inefficiency - ROS damages thyrocytes and impairs hormone synthesis	Forms a vicious cycle, worsening systemic dysfunction in DS individuals	(Ndakotsu et al., 2024)
Rationale for Review	Scientific Justification	- Integrated understanding of thyroid-oxidative stress axis lacking - Need for mechanistic insight and clinical translation	Supports the development of targeted diagnostics and interventions for DS-related comorbidities	(Santoro et al., 2022)

2. THYROID PHYSIOLOGY AND DYSFUNCTION IN DOWN SYNDROME

2.1 Normal Thyroid Physiology

Trisomy 21's gene dosage imbalance is the main source of oxidative stress in DS. Superoxide dismutase 1 (SOD1), a gene that codes for an enzyme involved in the conversion of superoxide radicals into hydrogen peroxide, is one of the important genes in this context. This may seem beneficial at first, but if hydrogen peroxide accumulation is not adequately neutralized by glutathione peroxidase or catalase, it can lead to oxidative damage by continuing to produce reactive oxygen species (ROS). Chronic oxidative stress disrupts signalling and cellular integrity by damaging proteins, lipids, and nucleic acids. The pathophysiology of several DS-related illnesses, including neurodegeneration, cardiovascular abnormalities, and endocrine dysfunction, is exacerbated by mitochondrial impairment, which intensifies ROS production and initiates a self-generative cycle of oxidative damage (Rodríguez-Sureda et al., 2015).

2.2 Lipid Peroxidation Markers in DS

The oxidative degradation of lipids, and most frequently polyunsaturated fatty acids, in cell membranes is known as lipid peroxidation. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), two hazardous aldehyde compounds produced by the process, can cross-link proteins, alter membrane fluidity, and interfere with cellular communication (Lanzillotta et al., 2021). High levels of MDA and 4-HNE have consistently been found in DS patients' plasma, red blood cells, and cerebrospinal fluid. Along with increased oxidative stress, these indicators also show damage to lipid membranes, which may be the cause of systemic inflammation and neuronal dysfunction (Tiano et al., 2008).

2.3 Deficits in Antioxidant Capacity

Other antioxidant defence system components are downregulated or functionally compromised in DS, in contrast to the increase of SOD1. These include dietary antioxidants such as vitamins C and E, glutathione (GSH), glutathione peroxidase (GPx), and catalase. Cellular compartments become more susceptible to oxidative damage when these vital enzymes and cofactors are depleted because it makes it more difficult to neutralize ROS. Furthermore, decreased GSH levels impair the body's capacity to detoxify, exposing cells to reactive intermediates for longer periods of time. Overall, the result is a state of persistent oxidative stress that exacerbates age-related cognitive decline and helps DS patients develop Alzheimer-like disease earlier (Garlet et al., 2013).

2.4 Neurological Consequences of Oxidative Damage

The central nervous system is one of the most important organs affected by oxidative stress in DS. Neurons' high oxygen consumption and limited ability to regenerate make them particularly vulnerable to oxidative injury (Helguera et al., 2013). Lipid peroxidation products, protein carbonylation, and DNA oxidation in the brain have been cited as contributing to the early development of Alzheimer's disease, which occurs in a large percentage of adults with DS by the fourth decade (Revilla et al., 2020).

Figure 1 illustrates the main causes of oxidative stress in people with Down Syndrome(DS), the combined effects of lipid peroxidation, deficiencies in the antioxidant system, and imbalances in gene dosage (e.g., overexpression of SOD1).

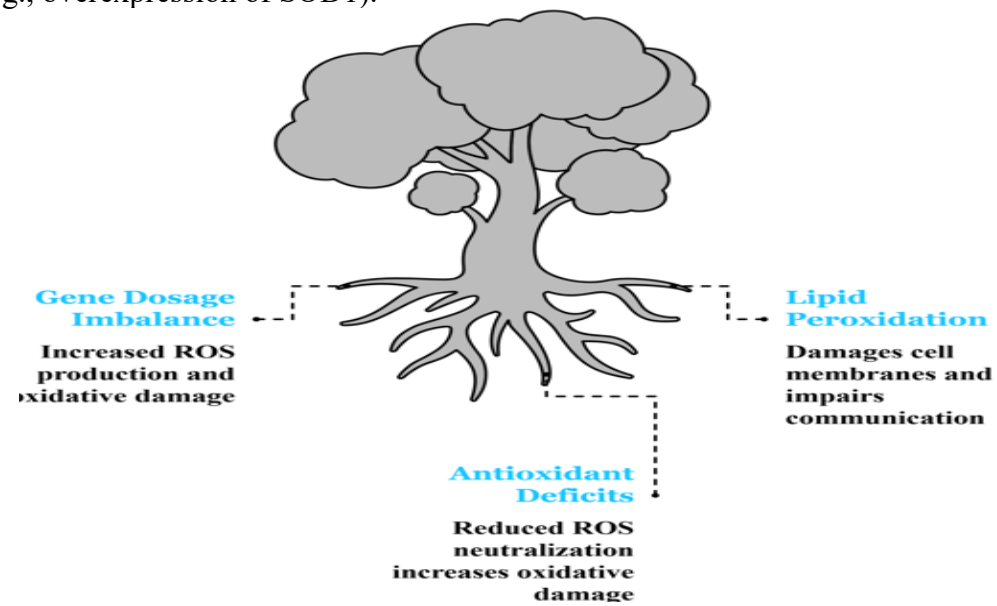

Figure 1. Mechanistic Contributors to Increased Oxidative Stress in Down Syndrome

3. INTERPLAY BETWEEN THYROID DYSFUNCTION AND LIPID PEROXIDATION

3.1 Thyroid Hormones and Oxidative Regulation

Thyroid hormones are essential for maintaining oxidative balance and mitochondrial efficiency. Dysfunctional mitochondrial respiration reduces ATP synthesis and increases ROS formation in hypothyroidism. This can improve apoptotic pathways and reduce cellular resilience to oxidative stress (Villanueva et al., 2013). Furthermore, T3 directly affects how antioxidant enzymes are regulated. Oxidative damage is exacerbated by hypothyroidism, which results in decreased transcription of these protective proteins. Thyroid dysfunction may significantly increase oxidative damage in DS when baseline antioxidant activity is already compromised.

3.2 Oxidative Stress Interfering with Thyroid Function

The loss of thyroid epithelial cells, or thyrocytes, may be a result of oxidative stress itself, which would interfere with the production and release of hormones. Thyroid gland cellular proteins and DNA may be oxidized by ROS, leading to autoimmune hypersensitivity, inflammation, and death. Oxidative damage has been shown in experimental models to increase the expression of major histocompatibility complex (MHC) in thyrocytes, increasing their immunogenicity and susceptibility to autoimmune thyroiditis. This mutual interaction results in a pathological cycle that is extremely destructive in the DS population, where thyroid dysfunction triggers oxidative stress, which in turn exacerbates thyroid damage (Helguera et al., 2013).

3.3 Correlative Evidence in DS

In individuals with DS, clinical research has shown a favourable correlation between elevated TSH levels and oxidative stress indicators such as MDA. The outcome lends credence to the idea that

oxidative damage and thyroid dysfunction are closely related. Both ailments may serve as targets for dual-modality therapies and biomarkers of the course of the illness.

The reciprocal link between thyroid hormones and oxidative stress in people with DS is depicted in Figure 2. While increased oxidative stress, which is caused by gene dosage effects and compromised antioxidant defences, can interfere with thyroid hormone production and glandular function, thyroid hormones are essential for controlling oxidative metabolism. Thyroid hormone-mediated oxidative control, oxidative stress-induced thyroid dysfunction, and clinical data demonstrating their association in DS pathophysiology are the three interconnected areas highlighted in the graphic.

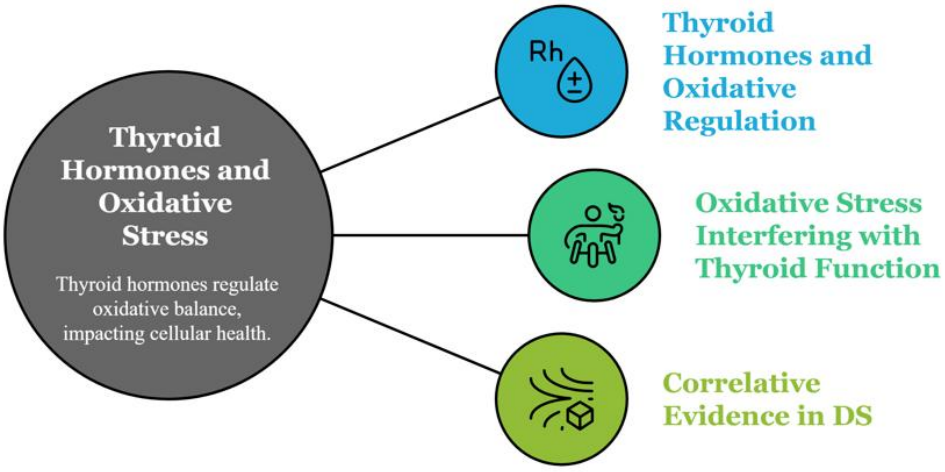

Figure 2. Unravelling the Thyroid-Oxidative Stress Nexus in Down Syndrome

4 THERAPEUTIC AND DIAGNOSTIC IMPLICATIONS

4.1 Early Screening Approaches

Mass screening initiatives are required due to the high incidence and chronic nature of thyroid dysfunction in DS. Although standard thyroid function test is performed on newborns, long-term follow-up is advised till youth and maturity, at least annually or every two years (Pierce et al., 2017). Early identification and the start of hormone replacement treatment are made possible by routine tests of thyroid autoantibodies, free T4, and TSH.

4.2 Follow-up of Oxidative Parameters

Oxidative stress may be measured biochemically by measuring free-circulating MDA, 4-HNE, and TAC. These indicators may be utilized to stratify the risk of problems and offer some insight into the redox status of DS patients. They also offer a way to gauge how well antioxidant treatments are working (Sarici et al., 2012).

4.3 Antioxidant-Based Interventions

The ability of several antioxidants, vitamins E and C, selenium, coenzyme Q10, and N-acetylcysteine to lessen oxidative stress in DS has been investigated. Due to variations in research design and treatment length, results are unclear, even though some studies report improvements in behavioural and oxidant parameters. Consequently, even if antioxidant therapy shows promise, it should be considered an adjuvant rather than a primary treatment.

4.4 Integrated Therapeutic Approaches

Thyroid hormone replacement medication and some antioxidant treatments may work in concert. The antioxidants reduce the ROS burden and restore euthyroid state, which both increase cell resilience and mitochondrial performance. Thyroid function tests and oxidative stress profiling can be used to customize treatment plans that may optimize DS outcomes, especially in halting or postponing the onset of neurological sequelae. Early screening procedures, biochemical indicators for redox

monitoring, adjunct medicines based on antioxidants, and integrated therapy models that include oxidative and hormonal management are all compiled in Table 2.

Table 2: Clinical Monitoring and Therapeutic Strategies

Domain	Strategy	Key Components	Clinical Rationale and Evidence	References
Early Screening Approaches	Longitudinal Thyroid Function Monitoring	- Newborn screening (TSH, fT4) - Autoantibody testing (anti-TPO, anti-Tg) - Annual or biennial reassessment	Early detection of congenital or acquired hypothyroidism is crucial due to its subclinical course and developmental implications. Routine screening enables timely levothyroxine initiation.	(Selikowitz, 2015; van Trotsenburg et al., 2006)
Follow-up of Oxidative Parameters	Redox Biomarker Assessment	- MDA (malondialdehyde) - 4-HNE (4-hydroxynonenal) - TAC (Total Antioxidant Capacity) - 8-OHdG (optional for DNA oxidative damage)	These markers provide insights into systemic oxidative status, treatment responsiveness, and stratify neurological risk. Elevated MDA and 4-HNE correlate with cognitive decline and mitochondrial dysfunction.	(MuchovÃ¡ et al., 2007; Tiano & Busciglio, 2011)
Antioxidant-Based Interventions	Adjunctive Redox Therapies	- Vitamin E - Vitamin C - Selenium - Coenzyme Q10 - N-Acetylcysteine (NAC)	Antioxidants have shown a reduction in oxidative stress biomarkers and mild cognitive/behavioral improvements. Efficacy remains variable due to inconsistent dosing, duration, and sample sizes.	(Nakanishi et al., 2012; Parisotto et al., 2015)
Integrated Therapeutic Approaches	Combined Hormonal and Antioxidant Modulation	- Levothyroxine + targeted antioxidant support - Periodic TSH, fT4, and redox marker testing.	Synergistic treatment supports mitochondrial efficiency, reduces ROS load, and may delay neurodegenerative progression in DS. Best outcomes observed with individualized treatment plans.	(Pinter et al., 2018; Izzo et al., 2020)

5. CRITICAL EVALUATION OF EXISTING LITERATURE

5.1 Limitations in Existing Research

Some limitations hamper the development of comprehensive clinical recommendations in the present research on the examination of thyroid dysfunction and lipid peroxidation in people with Down Syndrome(DS). Statistical power and the generalizability of findings are undermined by the small sample sizes used in some studies (Campos et al., 2011). Also, it is challenging to determine the cause and effect of oxidative stress markers and thyroid dysfunction because many studies are cross-sectional in design. Longitudinal studies are needed to determine how these conditions progress and affect one another. The assessment of the efficacy of intervention and the establishment of early biomarkers are impaired by the unavailability of longitudinal data (Convertini et al., 2016). 5.2 Variability of Diagnostic Threshold for TSH and fT4 in Down SyndromeThe diagnostic requirements employed in establishing thyroid dysfunction among patients with DS differ extensively. This disparity makes it difficult to develop uniform screening protocols and compare studies based on prevalence rates (Iughetti et al., 2014). There are differences in the prevalence figures since, for

instance, some studies define subclinical hypothyroidism by a TSH concentration greater than 5 mIU/L, while others employ greater values. In addition, research might not use age-adjusted reference values, and free thyroxine (fT4) measurements can have different values because there is no standardization in the measurement process. This lack of standardization may lead to misclassification of thyroid dysfunction among the DS group and excessive or inadequate treatment (Pepe et al., 2020).

5.3 Heterogeneity in Oxidative Marker Assays and Reference Ranges

Heterogeneity in the observed biomarkers and assays used restricts quantification of lipid peroxidation and oxidative stress in DS.

Research employs an array of markers of differential sensitivities and specificities, including protein carbonyls, isoprostanes, and malondialdehyde (MDA). In addition, interpretation of the data is further hindered by the fact that there are no established reference ranges for these biomarkers in the DS population. Variability in reported levels of oxidative stress can be explained by the variety of laboratory practices, including differences in sample handling, storage, and analysis. Making definitive judgments on the extent of oxidative damage and its clinical importance in DS people is made impossible by this discrepancy (Zitnanova et al., 2006). 5.4 Lack of Integrated Studies Investigating Endocrine and Redox Biomarkers Combined The fact that little research considers both thyroid function and oxidative stress markers in DS patients simultaneously is a strong literature limitation.

The majority of investigations consider either oxidative stress or endocrine pathologies, without noticing the possible interactions between the two systems.

The compartmentalized approach renders it more complicated to appreciate how oxidative damage and thyroid dysfunction correlate with each other, and vice versa (Campos et al., 2011). An explanation of the mutually dependent relationship between oxidative stress and thyroid hormones requires integral research. Such studies could present combination markers for early detection and treatment, in addition to synergistic effects that worsen clinical manifestations in DS.

5.5 Need for Standardized Procedures of Biochemical Measurement in Down SyndromePopulations

A high priority needs to be placed on standardizing tests for biochemical evaluation of oxidative stress and thyroid function in DS. As practices vary extensively, comparable treatments and diagnoses are lacking. Standardization of biomarkers, screening frequencies, and diagnostic thresholds would enhance clinical treatment through increased study comparability. Also, the validity of measurements would be enhanced by consideration of the individual's specific physiological profile in DS and application of age-specific reference intervals. Standardization would also enable us to perform large-scale epidemiological research and assess treatment strategies to reduce oxidative damage and thyroid disorder in this group (Molinari et al., 2024). Along with the needed methodological advancements, Figure 3 shows the existing research limitations in the study of thyroid dysfunction and oxidative stress in Down Syndrome(DS). It identifies significant issues such as non-standardized biomarker assays, diagnostic heterogeneity, and small sample sizes, and juxtaposes them with proposed solutions, including integrated frameworks, standardized protocols, and longitudinal studies. In order for DS treatment to yield replicable data and establish clinically applicable outcomes, these opposing factors should be reconciled.

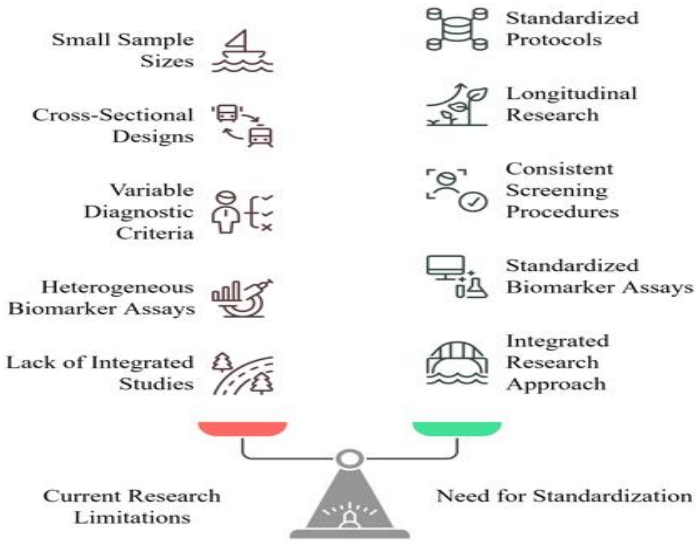

Figure 3. Balancing Research Limitations and Standardization Imperatives in Down SyndromeInvestigations

6. MOLECULAR MECHANISMS LINKING THYROID DYSFUNCTION AND OXIDATIVE STRESS IN DOWN SYNDROME

Down Syndrome(DS), which is characterized by trisomy 21, is linked to several physiological issues, including endocrine dysfunction and increased oxidative stress. Two of the most common and related biological disorders among them are oxidative damage and thyroid malfunction (Gillenwater et al., 2024). The complex molecular mechanisms linking these two disease fields are immunological dysregulation, mitochondrial dysfunction, gene expression modulation, and biochemical interactions between reactive oxidative species (ROS) and thyroid-specific enzymes. Understanding these molecular interactions is required to create personalized therapies targeting the immunological, neurological, and metabolic processes in DS patients (Izzo et al., 2018).

6.1 Dysregulated HPT Axis and Mitochondrial Respiration

One of the significant endocrine systems responsible for the manufacture and regulation of thyroid hormones, mostly thyroxine (T4) and triiodothyronine (T3), is the hypothalamic-pituitary-thyroid (HPT) axis.

These hormones play a vital role in thermogenesis, neurodevelopment, basal metabolic rate, and cellular respiration (Ortiga-Carvalho et al., 2011). Through the regulation of the transcription of nuclear and mitochondrial genes controlling oxidative phosphorylation, ATP generation, and reactive oxygen metabolism, they are able to modify their effects. In DS, this axis is frequently perturbed. Congenital and acquired hypothyroidism are increasingly prevalent, as evidenced by clinical and experimental data, due in part to feedback disrupted HPT axis. Decreased activity of important respiratory enzymes and mitochondrial uncoupling proteins is one of the mechanisms by which thyroid hormone deficiency compromises mitochondrial function. An excess of ROS are generated as a byproduct of inefficient ATP production and enhanced electron leakage from the mitochondrial electron transport chain (Villanueva et al., 2013). In addition, a thyroid hormone deficit could increase the oxidative load by inhibiting the synthesis of antioxidant enzymes like glutathione peroxidase and catalase. Basically, DS's disturbed endocrine communication leads to a compromised ability to utilize oxygen effectively as well as a heightened vulnerability to oxidative injury. This two-faced sword injures multiple organ systems, most significantly the immune and brain systems (Chow et al., 2017).

6.2 Gene Dosage Effects of Trisomy 21 (e.g., SOD1, APP, RCAN1) The gene dosage imbalance due to the trisomic presence of chromosome 21 is a very important molecular characteristic of DS. This chromosome harbours genes that are instrumental in ensuring mitochondrial integrity, immune

regulatory control, and redox balance. In this category, thyroid disorder and oxidative stress are connected by the overexpression of these genes.

The gene responsible for the enzyme superoxide dismutase 1 (SOD1) is one of the most studied. The superoxide radical (O_2^-) is converted to hydrogen peroxide (H_2O_2) by the enzyme. SOD1 overexpression in DS disrupts the delicate balance of the antioxidant defense system irrespective of the significance of SOD1 activity in reducing ROS. This creates a pro-oxidative cell wall environment through uneven $H2O_2$ deposition, especially when detoxification enzymes such as glutathione peroxidase and catalase are not increased in relative proportion. This encourages DNA damage, protein oxidation, and lipid peroxidation, especially in metabolically active tissues such as the brain and thyroid gland. The APP gene is yet another gene. Overexpression of APP boosts the production of neurotoxic amyloid-beta peptides, which can react with metal ions to produce reactive oxygen species (ROS). A cycle of oxidative damage is then perpetuated by the accumulation of amyloid-beta peptides, further disrupting energy metabolism and mitochondrial integrity (Singh et al., 2019). Chromosome 21's RCAN1 (Regulator of Calcineurin 1) also regulates immunological signalling and mitochondrial dynamics. Overexpression has been found to disrupt mitochondrial fusion and fission, which are important processes for maintaining cell homeostasis and mitochondrial function. RCAN1 also controls calcineurin and NF-κB pathways that are important for immunological activation and the response to oxidative stress.

When these genes are combined, an intracellular setting of high oxidative stress and mitochondrial susceptibility is established. Besides accelerating cellular senescence and death, this setting renders thyroid tissue more susceptible to autoimmune attack and functional destruction.

6.3 Inflammatory Cytokine Overexpression and Autoimmunity

The inflammatory immunological phenotype of DS patients is characterized by the chronic overexpression of numerous cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). Overexpression of interferon receptor genes (e.g., IFNAR1 and IFNAR2) on chromosome 21 is responsible for the increased inflammatory tone. Chronic production of inflammatory mediators results from the increased signaling cascades of the receptors. Due to its abundant vascularization and immunogenic antigens, the thyroid is particularly vulnerable to harm from inflammation. Major Histocompatibility Complex (MHC) class I and II molecules are expressed more on the surface of thyroid epithelial cells and can cause thyrocyte apoptosis. DS is linked to long-term exposure to cytokines. Autoimmune thyroiditis will be facilitated by this aberrant expression, which will increase the thyroid's recognition by immune cells (Ma et al., 2024).

Furthermore, inflammatory ROS can oxidize thyroid proteins such as thyroid peroxidase (TPO) and thyroglobulin, altering their antigenicity and potentially triggering the production of autoantibodies. This procedure is particularly important in DS because anti-TPO and anti-thyroglobulin antibodies are prevalent and typically manifest before the onset of clinical hypothyroidism. Additionally, oxidative stress can activate redox-sensitive transcription factors like as AP-1 and NF-κB, which maintain autoimmune cascades and increase the production of pro-inflammatory genes. In order to impair thyroid function and systemic metabolic regulation, the DS oxidative and inflammatory pathways are not independent but rather work in concert with one another (Aversa et al., 2015).

6.4 TPO Inhibition via Lipid Peroxidation Products (e.g., 4-HNE)

Lipid peroxidation, or the oxidative degradation of polyunsaturated fatty acids in cellular membranes, is one of the most harmful consequences of oxidative stress. Among the several reactive aldehyde products of lipid peroxidation, 4-hydroxynonenal (4-HNE) stands out because it has high reactivity and cytotoxicity (Zhong et al., 2015). 4-HNE is able to modify the protein structure and function by interacting with its nucleophilic residues to create covalent adducts. One of the primary targets of 4-HNE in the thyroid gland is thyroid peroxidase (TPO), a catalytic enzyme involved in iodide oxidation and organification, two obligatory events in the production of thyroid hormones. Covalent modification of TPO by 4-HNE could decrease the synthesis of T4 and T3 and impair its catalytic activity. Inhibition of TPO also causes overt and subclinical hypothyroidism. Immune cells can

become exposed to altered TPO epitopes, and hence the risk of autoimmune thyroiditis and autoantibody development. Furthermore, 4-HNE accumulation in thyroid tissue can aggravate local oxidative stress by inducing inflammatory responses and other ROS-generating mechanisms by way of feedback processes (Spickett, 2013).

According to experimental studies, 4-HNE exposure can cause mitochondrial malfunction and endoplasmic reticulum (ER) stress in thyroid cells, as well as inhibit hormone production and cell death. In DS, where 4-HNE baseline levels are elevated due to a combination of environmental and genetic causes, these effects are especially pronounced. Therefore, 4-HNE and other lipid peroxidation products are crucial molecular bridges that link thyroid dysfunction with oxidative stress. They are danger signals that improve immune surveillance and autoimmune development in addition to directly impairing enzymatic activity. The main molecular connections between oxidative stress and thyroid dysfunction in Down Syndromeare described in Table 3. These processes include thyroid enzymopathy caused by lipid peroxidation, cytokine-mediated immunological activation, mitochondrial and redox gene dysregulation, and endocrine disruption. Together, they explain the DS population's reciprocal aggravation of thyroid dysfunction and oxidative damage.

Table 3. Integrated Molecular Mechanisms Connecting Thyroid Dysfunction and Oxidative Stress in Down Syndrome

Mechanism	Molecular Players / Pathways	Functional Consequences	Implications for Down SyndromePathophysiology	References
Dysregulated Hypothalamic–Pituitary–Thyroid (HPT) Axis and Mitochondrial Respiration	TSH, T4, T3 Uncoupling proteins (UCPs) Cytochrome c oxidase (Complex IV) Antioxidant enzymes (GPx, CAT)	Impaired oxidative phosphorylation Reduced ATP synthesis Excess electron leakage and ROS generation Decreased mitochondrial efficiency	Disruption of the HPT axis in DS contributes to mitochondrial bioenergetic failure and elevated ROS burden, exacerbating neurodevelopmental and metabolic abnormalities.	(Villanueva et al., 2013; Ortiga-Carvalho et al., 2011)
Gene Dosage Imbalance from Trisomy 21	+SOD1: Increased conversion of O_2^- to H_2O_2 +APP: Aβ generation and metal-mediated ROS +RCAN1: Modulation of mitochondrial dynamics and NF-κB signalling	Imbalanced antioxidant response Accumulation of neurotoxic intermediates Altered mitochondrial fission/fusion Chronic pro-inflammatory signalling	Overexpression of redox-sensitive genes amplifies oxidative stress and primes immune activation, promoting thyroid dysfunction and CNS degeneration.	Izzo et al., 2018; Gillenwater et al., 2024
Cytokine Overexpression and Autoimmune Sensitization	IFN-γ, IL-6, TNF-αIFNAR1/2 overactivity NF-κB and AP-1 transcription factors MHC-I/II upregulation in thyrocytes	Enhanced antigen presentation ROS-mediated protein oxidation Autoantibody generation (anti-TPO, anti-Tg) Chronic thyroidal inflammation	A pro-inflammatory milieu and redox-modified thyroid antigens accelerate the onset of autoimmune thyroiditis, particularly in the preclinical stages of DS	(Aversa et al., 2015; Ma et al., 2024)
Lipid Peroxidation and Thyroid Enzyme Inhibition	4-Hydroxynonenal (4-HNE) Covalent attachment to TPO ER stress and mitochondrial damage pathways	Irreversible inactivation of TPO Impaired iodination and thyroid hormone synthesis Local tissue damage and immune amplification	Elevated 4-HNE levels in DS directly compromise TPO function and enhance immune recognition of altered epitopes, linking redox stress with thyroid autoimmunity.	(Zhong et al., 2015)

8. DIAGNOSTIC APPROACHES AND BIOMARKER STRATIFICATION

In order to recognize and monitor DS-related comorbidities over time, comprehensive awareness of endocrine and redox profiles is essential. Since DS patients possess a comparatively elevated incidence of thyroid disease and systemic redox disturbance, certain diagnostic tools exceeding reference population levels are needed. Since oxidative injury and endocrine disruption are synergistic and overlap in their clinical consequences, it is increasingly recognized that creating comprehensive diagnostic algorithms is key to better patient outcomes. While presenting current thyroid testing protocols, this section describes emerging diagnostic models, presents novel biomarkers of oxidative stress, and emphasizes challenges of biomarker validation and availability for clinical use in this special patient population (Zis et al., 2018).

8.1 Current practices in thyroid function testing in DS

High prevalence of congenital and acquired hypothyroidism in DS has introduced routine thyroid function monitoring as an integral part of clinical treatment of DS patients. Monitoring blood levels of free thyroxine (fT4) and thyroid-stimulating hormone (TSH) is a part of routine diagnostic evaluation. Typically, newborn screening programs test TSH from a heel-prick blood sample in the first few days of life to identify congenital hypothyroidism in neonates. TSH is still the most accurate first-line marker of thyroid abnormalities, although using it in DS requires clinical caution. The majority of DS patients have mildly to moderately elevated TSH levels without concomitant fT4 reductions, which is commonly referred to as subclinical hypothyroidism. Given that subclinical hypothyroidism can either heal on its own or progress in response to the presence of underlying autoimmune thyroiditis, this poses a clinical dilemma on whether to start levothyroxine therapy.

Measurement of thyroid autoantibodies, particularly anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies, is frequently included in follow-up evaluations to increase the clarity of the diagnosis. Even in borderline situations, the existence of these antibodies favors early pharmacologic intervention and points to an autoimmune cause. Furthermore, anatomical abnormalities like hypoplasia or ectopy may be shown by imaging modalities like thyroid ultrasonography, which helps guide treatment choices. According to current standards, thyroid function tests should be done annually between infancy and maturity, more frequently during times of rapid development, pubertal transition, or clinically significant endocrine instability (Vissenberg et al., 2015). Despite mounting evidence of the pathophysiological significance of oxidative stress indicators, these methods primarily concentrate on the hormonal axis and do not routinely employ them.

8.2 New Biomarkers of Redox Imbalance

In DS, oxidative stress is becoming recognized as a common Patho mechanism that causes endocrine disruption, particularly thyroid disturbance, as well as neurodegeneration and accelerated aging. Therefore, there is growing interest in both academic and clinical settings for the identification of stable biomarkers that represent the body's systemic oxidative load.

Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), lipid peroxidation products produced by the oxidative degradation of polyunsaturated fatty acids, are two of the most studied indicators. The plasma and erythrocytes of DS patients have been shown to exhibit elevated levels of MDA and 4-HNE, which correlate with clinical signs of metabolic disorders and cognitive impairment (Tolun et al., 2012).

Important redox indicators include protein carbonyl content, a sign of protein oxidation, and 8-hydroxy-2'-deoxyguanosine (8-OHdG), a sign of oxidative DNA damage. High disease load and rapid aging in DS have been linked to elevated levels of these indicators in the blood, urine, and cerebrospinal fluid. Another topic of research is antioxidant defence capability. An overall picture of the redox state is provided by monitoring the quantity of glutathione (GSH) and the enzyme activity of glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase. Even while gene triplication in DS increases SOD1 expression, downstream antioxidant systems are typically

overworked or dormant, creating an environment that seems to be pro-oxidative (Niedzielska et al., 2016).

A systems-level paradigm for the investigation of oxidative disturbances is offered by new redox biology methods, such as oxidative metabolomic profiling and redox-sensitive proteomics. Although their clinical application is still in its infancy, these high-throughput systems have the potential to identify novel biomarkers, therapeutic targets, and early predictors of organ-specific harm. Interestingly, there are significant associations between thyroid disease in DS and these redox markers (Ishihara et al., 2017). For example, elevated MDA levels are linked to low fT4 and high TSH, suggesting that oxidative damage may precede or occur concurrently with endocrine dysfunction. Such data support the use of redox biomarkers in standard diagnostic procedures for thyroid disorders linked to DS. The underutilization of redox indicators and a restricted hormonal emphasis are two major obstacles to an accurate comorbidity diagnosis in Down Syndromethat are depicted in this fishbone diagram. Additionally, it offers new approaches to enhance healthcare results, such AI-powered diagnostics and standardization (Figure 5).

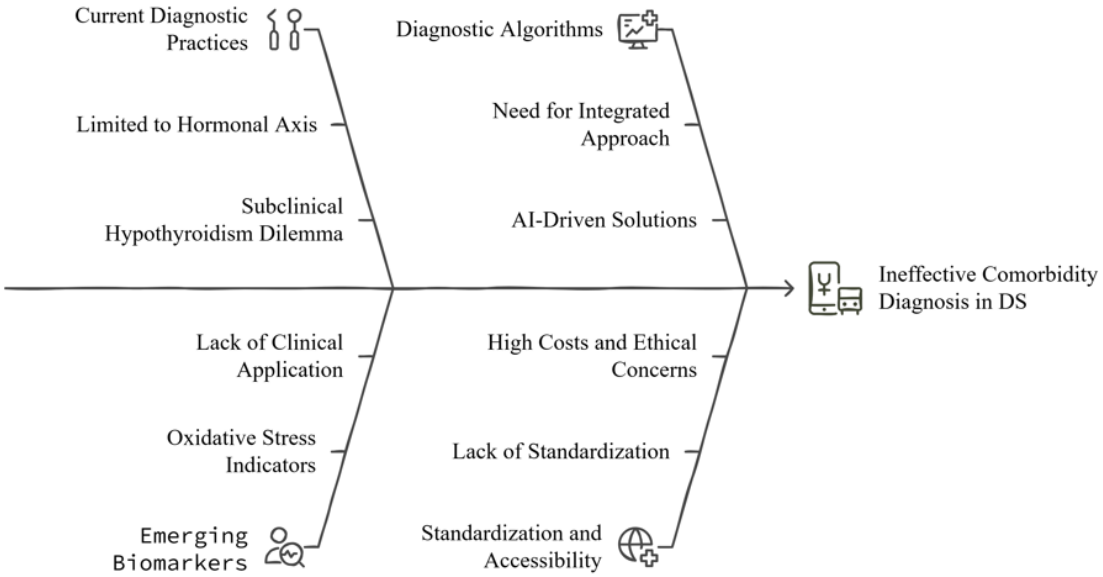

Figure 5. Diagnostic Challenges and Solutions for Comorbidity Detection in Down Syndrome

8.3 Diagnostic Algorithms That Combine Hormonal and Oxidative Indices

The subtleties of illness manifestation in DS can no longer be sufficiently captured by the antiquated division of diagnostics into endocrine and oxidative space. In order for doctors to detect patients at risk before clinical decompensation, there is a growing need for fused diagnostic algorithms that assess oxidative state and hormone function concurrently.

To assess thyroid status, a proposed multi-tiered strategy may begin with routine TSH and fT4 assays. Thyroid autoantibodies (anti-TPO, anti-Tg) would then be measured if the findings are abnormal or inconclusive, especially in cases of suspected autoimmune thyroiditis. To ascertain the systemic oxidative load, sets of oxidative biomarkers, such as MDA, 4-HNE, GSH, and GPx, would be assessed concurrently.

In addition to enabling the early detection of thyroid dysfunction, this approach would contextualize it within the broader oxidative milieu characteristic of DS. In contrast to a patient with similar TSH levels but normal oxidation indicators, a patient with slightly higher TSH, normal fT4, elevated MDA levels, and low GSH may be more likely to develop overt hypothyroidism or experience accelerated neurocognitive deterioration. Additionally, therapy may be guided by a combination of endocrine and oxidant markers (Uddin et al., 2019). Even in the absence of obvious symptoms, patients with increased oxidative stress and persistent subclinical hypothyroidism may need to start supportive antioxidant therapy and levothyroxine replacement therapy early. On the other hand, close monitoring

and frequent revaluation could be better for people with stable redox levels. Diagnostic solutions driven by artificial intelligence (AI) may potentially be able to include multidimensional biomarker data. Predictive insights into disease progression, treatment response, and risk stratification may be provided by machine learning-based algorithms that are trained on hormonal, redox, genetic, and clinical data. Even though they are still in the early stages of research, these technologies have the potential to completely transform DS precision diagnostics shortly.

8.4 Challenges in Biomarker Standardization and Accessibility

The biomarker research has advanced significantly and their theoretical appeal is increasing, several obstacles stand in the way of their practical translation and broad acceptance, especially in settings with limited resources or in paediatric populations with Down Syndrome(Ioannidis et al., 2017). Standardization remains a significant obstacle. For the study of redox biomarkers, laboratories employ a variety of techniques, reference periods, and sample treatment protocols. For example, the TBARS test, HPLC, or mass spectrometry can all be used to assess MDA; however, each has a unique set of specificities and sensitivities. Clinical decision-making is hampered and inter-study comparisons are impeded by the absence of commonly used cutoffs (McPartland, 2016). Furthermore, the majority of oxidative stress indicators are very variable and influenced by factors like as food, exercise, exposure to the environment, and circadian rhythm. Results will not be repeatable if rigorous pre-analytical controls are not in place. Before incorporating these tests into regular diagnosis, SOPs, reference ranges, and age-related standards for people with DS should be developed. Accessibility and cost are equally intimidating obstacles. Only universities and research institutes may use sophisticated techniques like metabolomics, proteomics, and multiplex immunoassays since they often require specialized equipment and skilled personnel. This is especially problematic in low-income nations when there is a high prevalence of DS but maybe inadequate healthcare infrastructure (Lee et al., 2017).

Furthermore, possible biomarkers still need to be clinically validated. Large-scale, longitudinal clinical trials are necessary to guarantee the predictive capacity, specificity, and responsiveness to intervention of the numerous promising compounds that have been identified by preliminary research. This solid evidence base will be required for regulatory body approval and inclusion in clinical recommendations (Smedinga et al., 2018). The ethical concerns of early biomarker testing in children present still another difficulty. When biomarkers are used for pre-symptomatic diagnosis of progressive disorders like early-onset Alzheimer's disease, conflicts including informed consent, data privacy, and psychological effects must be addressed with extreme caution (Porteri et al., 2017).

These challenges are not, however, insurmountable. Global consortia, such as the Global Biomarker Standardization Consortium and the Human Proteome Organization, are continuing their efforts to harmonize biomarker testing. Shortly, developments in miniaturized biosensor technology and point-of-care testing (POCT) might democratize access to advanced diagnostics by integrating them into routine paediatric and endocrinology clinics.

Despite significant progress in understanding the pathophysiologic underpinnings of Down Syndrome(DS), several questions remain, particularly at the intersection of oxidative stress, thyroid dysfunction, and multisystemic comorbidities (Alasmari et al., 2025). The need for an advanced research paradigm that goes beyond descriptive studies and single-biomarker analysis is highlighted by the growing recognition of the connections between these complex systems (Alldred et al., 2021). It will be necessary to move toward integrative, data-intensive, and customized research methodologies in order to achieve clinical gains in DS. Besides defining future directions towards precision diagnostics, treatment findings, and predictive modelling in DS, this chapter focuses on the most urgent research needs. It emphasizes how essential it is to integrate multi-omics platforms, longitudinal cohort studies, AI-driven interpretation, and the translation of these tools into precision medicine.

9. CONCLUSION

The intersection between thyroid dysfunction and oxidative stress in patients with Down Syndrome(DS) is a critical and underappreciated connection that impacts multiple domains of health, from neurodevelopment to metabolic homeostasis and cardiovascular disease risk. This review emphasizes the importance of how gene dosage compensation, specifically overexpression of SOD1, APP, and RCAN1 on chromosome 21, creates a cellular milieu of redox disequilibrium and mitochondrial dysfunction. Parallel with this is deranged regulation of the hypothalamic-pituitary-thyroid axis, contributing to levels of hypothyroidism, typically subclinical, but with significant clinical effects when not addressed or insufficiently treated. On the molecular level, there is a pathological bidirectional feedback loop apparent: thyroid hormone deficiency compromises antioxidant defences and mitochondrial activity, while oxidative damage promotes thyroid gland integrity and enzyme activity, particularly thyroid peroxidase. Such shared pathology is further enhanced by chronic inflammation and peroxidation of lipids, both of which donate to individuals with DS to premature neurodegeneration, disturbances in growth, and early-onset Alzheimer's disease. In light of these observations, however, existing clinical diagnostics frequently do not incorporate redox biomarkers into endocrine parameters, and therapeutic approaches remain mostly disjointed. Emerging priorities should include longitudinal, multi-omics-guided studies that integrate hormonal, oxidative, immunologic, and genetic profiling. By leveraging artificial intelligence and precision medicine platforms, such methodologies potentially can move beyond merely delayed detection to enable personalized treatment regimens, enhanced prognostic outcomes. Finally, the understanding of the interaction between thyroid dysfunction and oxidative stress in DS not only increases our knowledge of its multisystem pathology but also uncovers avenues towards anticipatory, targeted, and life-enhancing intervention for this susceptible population.

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