The Critical Interplay: Systemic Thyroid Regulation and Local Growth Factor Signaling in Male Infertility

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ABSTRACT

Male infertility is a major concern globally, creating significant health and emotional burdens for countless couples (World Health Organization [WHO]). While we know that male factors are responsible for about one-third of all infertility cases, they are actually involved in nearly half of all presentations. This paper suggests that the root cause is not simply genetic or structural issues, but a complicated combination of large-scale endocrine problems and localized stresses at the cellular level. Our analysis focuses on three components that are connected in this process: the strong but often overlooked influence of the neuroendocrine thyroid system, the vital local signaling provided by growth factors such as Insulin-like Growth Factor 2 (IGF2), and the potential for a localized treatment like Platelet-Rich Plasma (PRP). We synthesize existing data that ties even minor thyroid hormone issues, particularly subclinical hypothyroidism (SCH), to measurable damage in key sperm parameters. Furthermore, we explore how local signals, specifically \IGF2, regulate the essential cell processes for healthy sperm development by interacting with pathways related to inflammation and oxidative stress (OS). Finally, we briefly look at the potential of PRP, which is rich in these repairing growth factors, as a localized approach to reduce the damage from OS on sperm cells. This integrated perspective highlights a clear need for a broad, holistic diagnostic and management strategy in clinical andrology.

Keywords: *Oxidative Stress, Andrology, Insulin-Like_Growth Factor, Sperm, Particulary Subclinical Hypothyroidism, Platelet-Rich Plasma, Male Infertility*

1. *INTRODUCTION*

Infertility, commonly defined as the inability to conceive naturally after a year of trying, impacts a substantial portion of the global population, estimated at 8% to 15% of couples (WHO, 2023; Borght & Wyns, 2018). It is now universally recognized that issues originating from the male partner contribute to approximately 50% of these cases, cementing male-factor infertility as an ongoing clinical priority (Agarwal et al., 2015; Stephen & Chandra, 2006). The clinical picture of male infertility is diverse, mainly arising from defects in the process of sperm production (spermatogenesis). These range from no sperm at all (azoospermia) to low numbers (oligospermia) or defects in movement (asthenospermia) and shape (teratozoospermia) (Tang et al., 2025; La Vignera & Vita, 2018). Given that these dysfunctions have so many different underlying causes, current research has appropriately moved past just checking semen samples. The focus is now on understanding the hidden molecular and neuroendocrine disruptions that truly govern testicular function and health (Soureshjani et al., 2025; Babatunde & Emokpae, 2024).

It is increasingly apparent that healthy sperm production depends on a tightly managed balance. This balance occurs between systemic hormone signals (primarily regulated by the hypothalamic-pituitary-gonadal (HPG axis) and the local environment within the testis. Two regulatory pathways specifically, the connection between the thyroid and the HPG axis and the local control exerted by growth factors are now seen as having central roles in supporting the delicate microenvironment required for successful reproduction (Gabrielson et al., 2019; Tang et al., 2025).

2. Thyroid and Neuroendocrine Factors: The Systemic Regulator

For a considerable time, the effects of thyroid dysfunction on the male reproductive system were significantly underestimated in routine infertility evaluations (Babatunde & Emokpae, 2024; Gabrielson et al., 2019). However, we now have a much clearer picture of the critical and widespread influence of the thyroid gland, whose hormones are involved in basic metabolism and regulating sex hormone production (La Vignera & Vita, 2018). When the necessary interaction between systemic thyroid hormones and the HPG axis is significantly disrupted whether by an overactive or underactive thyroid the hormone balance required for effective sperm production and fertility is put at risk (Babatunde & Emokpae, 2024; Corrales-Hernandez et al., 1990). This can trigger a range of minor hormone imbalances that are relevant to infertile male patients (Esan et al., 2022).

Thyroid-Stimulating Hormone (TSH), which comes from the pituitary gland, is a key regulator directly linked to male fertility. Non-normal TSH levels (both higher and lower than normal) are consistently associated with harmful effects on semen quality (Soureshjani et al., 2025). Studies have shown clear relationships between TSH level problems and a measurable decrease in both sperm count and concentration (Soureshjani et al., 2025; La Vignera & Vita, 2018). Even more concerning is the link between poor TSH regulation and damage to genetic integrity, often resulting in increased sperm DNA fragmentation (Zhao et al., 2022). This systemic hormone problem is also thought to directly impair essential functional sperm activity, potentially leading to reduced progressive motility and viability (Babatunde & Emokpae, 2024; Soureshjani et al., 2025). Given this growing body of evidence, the routine evaluation of thyroid hormone and TSH levels is becoming an essential part of the standard diagnostic process for men facing infertility (Gabrielson et al., 2019).

2.1 The Effect of Subclinical Hypothyroidism (SCH)

While we know a lot about the severe impact of overt hypothyroidism on testis function, recent, detailed studies have intensely focused on the common, yet easily missed, condition known as subclinical hypothyroidism (SCH) (Bahreiny et al., 2025). SCH is defined by serum TSH levels that are elevated, even though circulating levels of free thyroxine (fT4) and triiodothyronine (T3) are still technically within the normal reference range (Bahreiny et al., 2025; Zhao et al., 2022). A highly detailed meta-analysis, which included data from ten studies and over 2,239 participants, firmly concluded that SCH does, in fact, significantly compromise various critical sperm quality parameters (Bahreiny et al., 2025). The combined evidence from this meta-analysis indicated a notable negative effect across several diagnostic markers (Bahreiny et al., 2025). Specifically, there was a statistically significant decrease in total sperm count (Standardized Mean Difference [SMD] = -0.604, P=0.039) and a clinically important reduction in progressive motility (SMD = -1.437, P < 0.001) (Bahreiny et al., 2025). Furthermore, sperm morphology which is a strong predictor of fertilization success was also negatively affected (SMD = -0.784, P=0.013) (Bahreiny et al., 2025). These definitive and statistically robust findings highlight the clinical need to consistently include thyroid function screening as an essential step in the diagnosis and management of male infertility (Babatunde & Emokpae, 2024).

3. Growth Factors and Spermatogenesis: The Local Context

In addition to the crucial systemic control from the thyroid-HPG axis, a local, highly regulated signaling network driven by growth factors is absolutely necessary for maintaining normal testis function and orchestrating the complex process of sperm production (Tang et al., 2025). When spermatogenesis goes wrong, leading to male infertility, it is closely related to the presence of chronic cellular stresses within the seminiferous tubules. These include inflammation, ER stress, and particularly oxidative stress (OS) (Tang et al., 2025; Sanocka & Kurpisz, 2004). This complex condition can stem from genetic issues or a range of acquired factors (Tang et al., 2025). The acquired factors, which make up a large portion of clinical cases, include varicocele, infections, exposure to toxic chemicals, and unhealthy lifestyle choices (Tang et al., 2025). It is precisely in the context of mitigating these acquired, stress-induced issues especially those involving chronic inflammation and intense OS that the protective and regulatory roles of key local molecules become most important (Tang et al., 2025; Agarwal et al., 2014; Aprioku, 2013).

3.1 The Regulatory Role of Insulin-like Growth Factors (IGF-1 and IGF2)

The Insulin-like Growth Factors (IGFs) have emerged as particularly important molecules whose local activity is deeply linked to the factors causing spermatogenesis problems (Tang et al., 2025). IGF2 is currently the focus of considerable study because of its theoretical and experimental capacity to potentially prevent or treat male infertility, largely by acting on major cell stress pathways (Tang et al., 2025). Furthermore, IGF-1 is also known to be important in the male reproductive system, with initial evidence suggesting that administering it might help improve sperm quality and fertility in men with various reproductive issues (Metallinou et al., 2024).The literature indicates a direct connection between IGF2 and the core problems in spermatogenesis, including inflammation, ER stress, and especially oxidative stress (Tang et al., 2025). The proposed mechanism involves controlling the anti-cell-death and anti-inflammatory signaling pathways within the germ and Sertoli cells of the testis (Tang et al., 2025). By intervening in these pathways, IGF2 shows potential for reversing the chronic damage from environmental or acquired stressors, thus offering a molecular reason for its possible therapeutic use in shielding the sensitive sperm lineage from harm (Tang et al., 2025). Other growth factors such as NGF and EPO are also involved in regulating sperm function, particularly its motility and survival, emphasizing the breadth of local signaling in the testis (Metallinou et al., 2024).

4. Oxidative Stress and Localized Reparative Interventions

Oxidative stress (OS), which is essentially when the excessive production of reactive oxygen species (ROS) overwhelms the body's natural antioxidant defenses, is now recognized as a major contributing factor in a large proportion 30% to 80% of all male infertility cases (Cho & Agarwal, 2018; Sigman et al., 2009; Sanocka & Kurpisz, 2004). High levels of ROS are known to cause severe, multi-level damage to sperm cells. This damage includes breaking down the plasma membrane through lipid peroxidation and crucially, causing sperm DNA fragmentation (Aprioku, 2013; Benchaib et al., 2007).
In the ongoing search for effective treatments to neutralize the damaging effects of chronic OS, Platelet-Rich Plasma (PRP) has quickly gained attention as a promising, entirely autologous (using the patient's own blood) therapeutic strategy (Bader et al., 2020). PRP is prepared as a platelet concentrate containing a rich and powerful mix of reparative growth factors, which are stored and released mainly from within the alpha granules of the platelets (Bader et al., 2020).

An important in vitro study specifically investigated the effects of PRP on human sperm exposed to artificially induced OS (Bader et al., 2020). The results showed a compelling ability for PRP to substantially improve overall sperm quality, especially when the cells were challenged with H2O2-induced oxidative stress (Bader et al., 2020). This powerful protective action is logically attributed to the array of growth factors within PRP (Bader et al., 2020). These growth factors are thought to contribute significantly to the inhibition of ROS through their inherent antioxidant and anti-apoptotic (anti-cell-death) activities, thereby protecting the vulnerable sperm cells (Bader et al., 2020; Aprioku, 2013). Overall, the positive effects of PRP strongly suggest its potential for future clinical use as a novel,

localized agent to counteract the damaging effects of OS on male reproductive cells (Bader et al., 2020; Sigman et al., 2009).

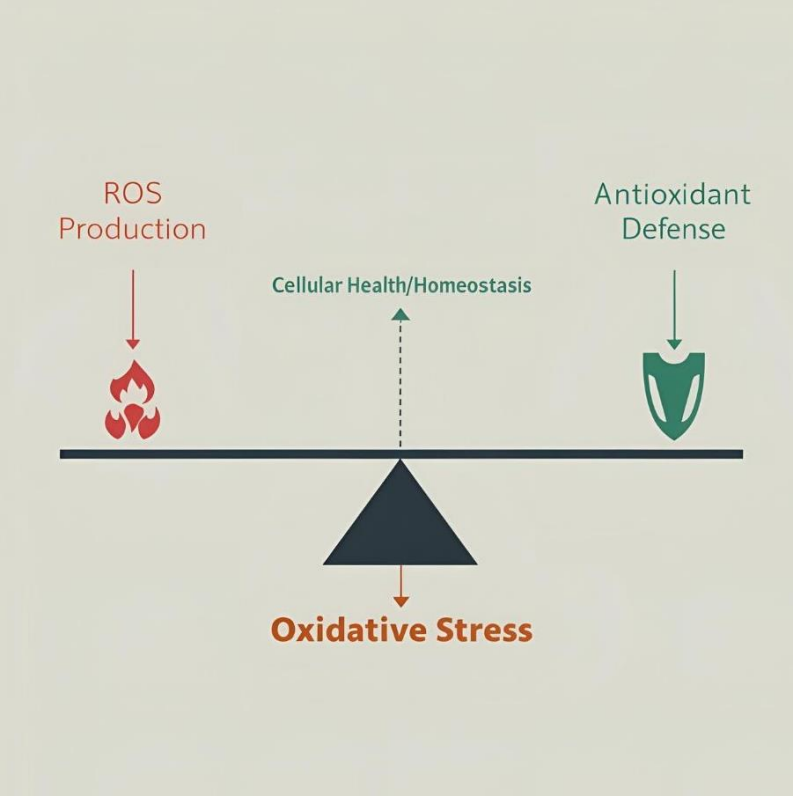

Fig. 1. Cellular Oxidative Balance, A simplified schematic illustrating the oxidative balance within a cell and the pathway to oxidative stress. This figure demonstrates the delicate equilibrium between the production of Reactive Oxygen Species (ROS) and the antioxidant defense system (including antioxidant enzymes and molecules). In a healthy state (Homeostasis), this balance is maintained. Any disruption of this balance in favor of ROS leads to oxidative stress, damage to cellular macromolecules, and ultimately chronic diseases.

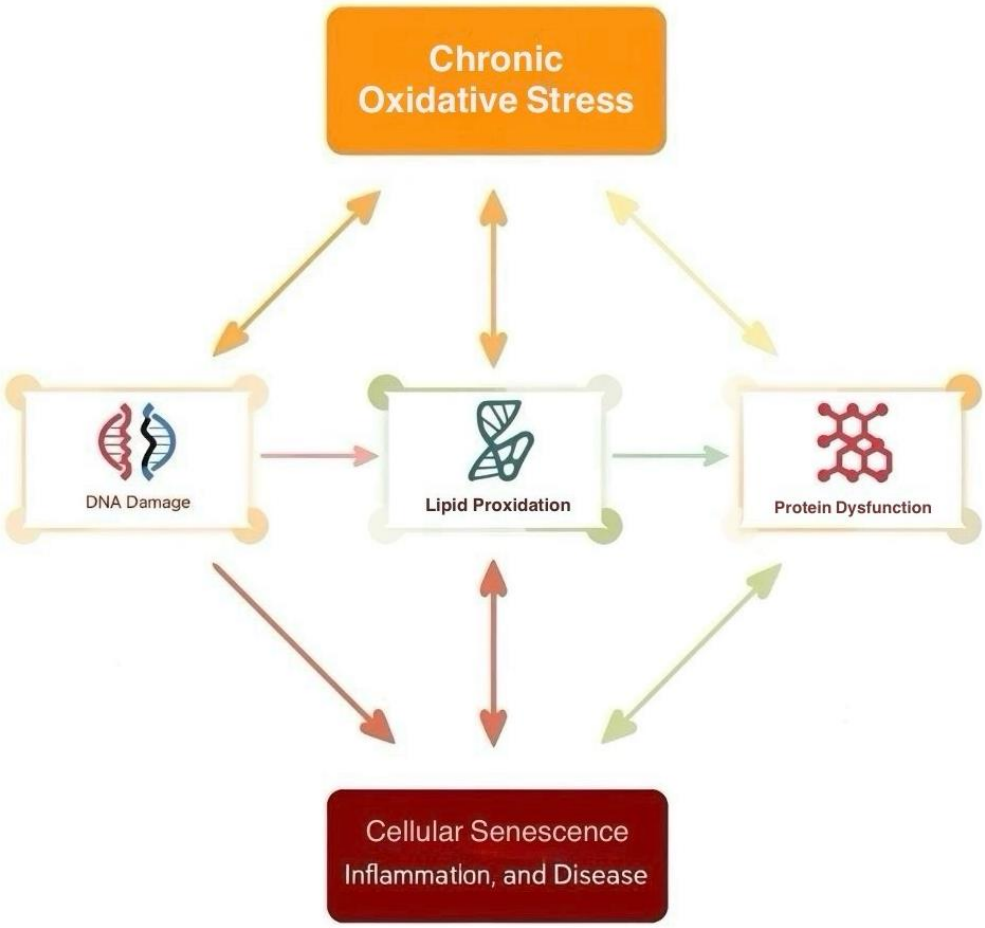

Fig. 2. Consequences of Chronic Oxidative Stress, A flowchart detailing the pathological consequences of chronic oxidative stress. Persistent oxidative stress is a key driver that directly damages vital cellular macromolecules. These damages include DNA degradation, alteration of protein structures, and oxidation of cell membrane lipids, ultimately leading to mitochondrial dysfunction, activation of inflammatory pathways, and accelerated cellular senescence. This process acts as an underlying factor in many age-related diseases.

5. Conclusion and Future Perspectives

Our review of the current literature firmly supports the idea that viewing male infertility in a simplistic, narrow way is clinically insufficient (Babatunde & Emokpae, 2024; Tang et al., 2025). The strongest evidence suggests that the underlying problem results from a complex and challenging combination of systemic hormone issues and intense local cellular stresses (Soureshjani et al., 2025; Tang et al., 2025). The data confirms that even minor thyroid problems, notably the easily missed subclinical hypothyroidism (SCH), pose a clear and statistically significant risk to key sperm parameters like morphology, motility, and count (Bahreiny et al., 2025; Zhao et al., 2022). Simultaneously, essential local growth factors such as IGF2 and IGF-1 are fundamentally important in managing the complex cellular response to the oxidative and inflammatory stresses that constantly harm sperm (Tang et al., 2025; Metallinou et al., 2024).

By connecting the systemic regulation (the thyroid axis) with effective local intervention, the study of Platelet-Rich Plasma (PRP) a practical and local source of therapeutic growth factors points to an exciting new path in translational andrology (Bader et al., 2020). PRP's documented ability to significantly improve motility and reduce the severe damage from oxidative stress, a very common issue

in infertile men, must be followed up with further large-scale in vivo and comprehensive clinical trials (Bader et al., 2020).

Future research must specifically focus on clearly defining the exact molecular pathways through which IGF2 and the mixture of growth factors in PRP achieve their protective effects (Tang et al., 2025). Critically, the field must determine whether routine, universal thyroid function screening, extending beyond obvious disease, should be officially added to the initial diagnostic protocol for all infertile men (Babatunde & Emokpae, 2024; Bahreiny et al., 2025). Achieving a complete and integrated understanding of these interconnected regulatory mechanisms is the necessary next step to refine current treatments and ultimately improve fertility outcomes globally (Agarwal et al., 2015; WHO, 2023).

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