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The Background of Varicocele-Related Infertility

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ABSTRACT

Purpose: The aim of this narrative review is to evaluate the molecular and cellular effects of varicocele on male infertility from a holistic perspective. The study examines the role of varicocele on spermatogenesis and testicular homeostasis, specifically within the axis of oxidative stress, apoptotic mechanisms, hormonal changes, epigenetic regulations, and the ubiquitin–proteasome system (UPS).
Methods: A comprehensive literature search was conducted in PubMed, Web of Science, Scopus, and Google Scholar databases for the period between 1973 and 2025 using the keywords "varicocele," "male infertility," "oxidative stress," "apoptosis," and "ubiquitin proteasome system." Case reports and irrelevant publications were excluded, and the molecular, histopathological, and hormonal effects of varicocele were systematically reviewed.
Results: The findings indicate that varicocele leads to increased oxidative stress and mitochondrial dysfunction within the testicular microenvironment. This process is associated with sperm DNA damage, loss of motility, and morphological abnormalities. While increased apoptosis triggers germ cell loss and spermatogenesis impairment, a decrease in Leydig cell function results in reduced testosterone production. Furthermore, varicocele alters the epigenetic profile through DNA and RNA methylation and histone modifications; UPS dysfunction impairs protein homeostasis, adversely affecting sperm maturation and function. Histopathological examinations reveal degeneration in the seminiferous tubules, basement membrane thickening, and significant changes in Sertoli–Leydig cell structure.
Conclusions: Varicocele is not merely a vascular disorder but a multidimensional cause of infertility arising from the interaction of oxidative stress, apoptotic activation, hormonal imbalance, epigenetic disruption, and UPS dysfunction. By synthesizing the molecular and histopathological mechanisms of varicocele, this review emphasizes the importance of early diagnosis and targeted clinical approaches.

Keywords: Varicocele, Male infertility, Testicular damage, Spermatogenesis, Ubiquitin proteasome system

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Introduction

Varicocele is one of the most common causes of male infertility. Characterized by dilation of the pampiniform plexus and internal spermatic veins, varicocele was first described by the Roman Celsus in the first century, and the first varicocelectomy was performed approximately 200 years ago by the French surgeon Delpech (1, 2). Although the mechanism underlying varicocele and impaired testicular function has not been fully elucidated, an increase in intratesticular temperature has been suggested as a significant factor (3, 4). It is well established that the pampiniform plexus within the spermatic cord regulates heat exchange through a "countercurrent" mechanism between arterial and venous blood flow, playing a critical role in testicular thermoregulation. As arterial blood enters the testis, it is cooled by venous blood, thereby maintaining a low testicular temperature. In the presence of varicocele, this mechanism is disrupted, and venous blood fails to adequately cool the arterial blood. This relationship was first demonstrated in 1971, and it was suggested that even unilateral varicocele could exert bilateral effects (5). In light of these studies, the etiology of varicocele and the mechanisms leading to infertility remain incompletely understood. Despite numerous theories proposing how varicocele affects spermatogenesis and leads to its impairment, a consensus has yet to be achieved. Recent studies have suggested that varicocele may trigger apoptosis in reproductive cells, and that increased apoptosis may contribute to infertility by reducing sperm concentration (6, 7).

Varicocele, considered the most frequently correctable pathology in male infertility, is observed in approximately 15% of the general population (8). Among men presenting with primary infertility, the prevalence of varicocele has been reported to be around 35% (9). This rate increases to 70–80% among men with secondary infertility, and varicocele is regarded as the most common cause of secondary infertility (10). Despite the high prevalence of varicocele in the general population, only approximately 20% of men are infertile, while fertility remains unaffected in the remaining 80%, highlighting the need for further research to elucidate the pathophysiological mechanisms linking varicocele and infertility (11). While some studies have indicated that varicocele is absent in children under 10 years of age and its prevalence increases between 10 and 14 years, suggesting that varicocele develops only during puberty (12), the findings of a comprehensive prevalence study conducted by Akbay et al. on 4,052 children aged 2–19 years indicate that varicocele may also begin at an early age (13). According to this study, the prevalence of varicocele is 0.92% in the 2–10-year age group and reaches 11% during adolescence (11–19 years). These findings suggest that varicocele is not solely associated with advanced-stage infertility; early-onset testicular damage may accumulate over time, predisposing to long-term fertility loss. In this context, early identification of subclinical molecular changes, detection of potentially reversible testicular damage, and timely intervention are clinically important. In particular, evaluating oxidative stress markers, epigenetic profiles, and components of the ubiquitin–proteasome system (UPS) as potential biomarkers may contribute to optimizing patient selection and timing of treatment.

Recent studies indicate that varicocele leads to increased oxidative stress in the testicular microenvironment, activation of apoptotic pathways, hormonal imbalance, as well as significant disruptions in the ubiquitin–proteasome system (UPS) and UPS-related epigenetic processes, which play critical roles in cellular protein homeostasis and chromatin organization (14). However, how these molecular processes interact and collectively contribute to the development of varicocele-associated infertility has not yet been clearly defined. This narrative review aims to address the molecular pathophysiology of varicocele within a comprehensive framework encompassing oxidative stress, apoptosis, hormonal alterations, and particularly the UPS axis. This approach is intended to fill the existing knowledge gap regarding the molecular basis of sperm function and testicular homeostasis, providing a contemporary and integrative perspective to the field.

Materials and Methods

This narrative review was prepared to evaluate the effects of varicocele on male infertility based on oxidative stress, apoptosis, endocrine alterations, epigenetic regulation/ubiquitin–proteasome system (UPS), and histopathological findings. A literature search was conducted

using PubMed, Web of Science, Scopus, and Google Scholar databases, including studies published between 1973 and 2025. During the search, keywords such as “varicocele,” “male infertility,” “testicular histopathology,” “spermatogenesis,” “oxidative stress,” “apoptosis,” and “ubiquitin–proteasome system,” along with their combinations, were employed. Clinical and experimental studies providing information on varicocele pathophysiology, testicular microenvironment, hormonal and molecular alterations, and effects on spermatogenesis were included; case reports, editorial articles, and publications outside the scope of the topic were excluded. The broad time frame was chosen to ensure conceptual continuity between classical pathophysiological findings and contemporary molecular mechanisms.

1. Overview of Varicocele Pathophysiology

Varicocele is known to cause progressive and time-dependent testicular damage in both animal models (15, 16) and humans (17). The World Health Organization (WHO), examining the effects of varicocele on fertility, explicitly emphasizes that the condition is associated with semen abnormalities, such as decreased sperm count and impaired motility, as well as reductions in testicular volume and Leydig cell function (18). The pathophysiological effects occur through multidimensional processes, including oxidative stress and mitochondrial dysfunction in the testicular microenvironment, activation of apoptotic and other cell death mechanisms, hormonal dysregulation, epigenetic modifications, and functional impairment of protein degradation pathways mediated by the ubiquitin–proteasome system (UPS).

1.1. Oxidative Stress and Mitochondrial Dysfunction

Among reactive oxygen species (ROS) are superoxide anions, hydroxyl radicals, nitric oxide, hypochlorous acid, and hydrogen peroxide. When incubated under aerobic conditions, human spermatozoa possess the capacity to generate ROS (19). ROS production by spermatozoa is a physiological process that plays a critical role in signal transduction mechanisms, sperm hyperactivation and capacitation, facilitation of the acrosome reaction, and sperm–oocyte fusion (20,21). In healthy individuals, seminal plasma contains natural scavengers or antioxidants that neutralize the effects of excessive ROS production. However, under pathological conditions, ROS production exceeds antioxidant capacity, leading to elevated oxidative stress (20, 22, 23, 24). ROS can induce lipid peroxidation of polyunsaturated fatty acids in the sperm head and midpiece, resulting in defective sperm function, impaired morphology, reduced motility, and insufficient sperm–oocyte fusion (25,26). Additionally, ROS may cause sperm DNA damage. Evaluations of semen samples from fertile and infertile men with varicocele have demonstrated higher ROS concentrations compared to men without varicocele (27). Increased ROS concentration was observed in 80% of infertile varicocele cases, 77% of fertile men with varicocele, and 20% of fertile men without varicocele. Moreover, total antioxidant capacity was significantly higher in normal individuals compared to those with varicocele (28). One study also indicated that susceptibility to oxidative stress is increased due to a marked reduction in fatty acid content in the sperm plasma membrane (29). Varicocele increases oxidative stress in the testicular microenvironment due to dilation of the testicular veins and impaired testicular blood flow. Oxidative stress is characterized by excessive production of ROS, which directly damages germ cells as well as sperm lipid membranes, DNA, and protein structures. Mitochondria in sperm cells play a critical role in ROS generation while providing ATP required for energy production. Mitochondrial dysfunction results in disruptions of the electron transport chain and insufficient energy production, adversely affecting both sperm motility and viability.

Elevated ROS levels and mitochondrial dysfunction trigger apoptotic pathways in germ cells and impair spermatogenesis. This manifests as reduced sperm count, loss of motility, morphological abnormalities, and compromised DNA integrity. Furthermore, mitochondrial dysfunction can negatively affect androgen production and Leydig cell function through cellular energy depletion, which, combined with hormonal imbalance, reinforces infertility. In conclusion, oxidative stress and mitochondrial dysfunction are recognized as central pathophysiological mechanisms in varicocele-associated infertility, impacting testicular function and sperm quality. These processes play critical roles in spermatogenesis

at both cellular and molecular levels and provide a foundational framework for understanding the detrimental effects of varicocele on fertility.

1.2. Activation of Apoptotic Cell Death Mechanisms

The relationship between varicocele and apoptosis is primarily explained through three major pathophysiological mechanisms: heat stress, androgen deficiency, and exposure to toxic stimuli (30). These mechanisms lead to increased programmed cell death in germ cells as a result of the disruptions varicocele induces in the testicular microenvironment.

The increase in intratesticular temperature caused by varicocele is one of the earliest identified mechanisms associated with apoptosis. In a study by Lue et al. (31), testicular heat elevation was shown to induce stage-specific apoptotic responses in germ cells, indicating that certain phases of spermatogenesis are more sensitive to thermal stress. This finding is clinically significant, given the high sensitivity of spermatogenesis to temperature. Heat stress disrupts mitochondrial membrane integrity, triggers cytochrome c release, and activates the caspase cascade, forming the molecular basis of the heat–apoptosis relationship in varicocele. Programmed cell death is not only a pathological phenomenon but also a normal component of physiological spermatogenesis. Literature reports (32) emphasize that apoptosis maintains testicular homeostasis by regulating the balance between germ cell numbers and the supportive capacity of Sertoli cells. Similarly, a certain level of germ cell elimination is essential for normal sperm development; Kerr reported continuous spontaneous apoptotic activity in the testis (33). In pathological conditions such as varicocele, this physiological process becomes excessively activated, disrupting spermatogenesis.

Recent experimental and clinical studies indicate that increased and dysregulated apoptosis due to varicocele plays a critical role, particularly in the pathogenesis of oligospermia. In a rat model study by Barqawi et al., 14 days after varicocele induction, an average of 0.23 apoptotic cells per seminiferous tubule was detected, significantly higher than in the control group (34). Similar results have been reported in humans, with the proportion of apoptotic germ cells at 14.7% in varicocele cases compared to 2% in controls (35). Another study examining ejaculated sperm found that up to 10% of spermatozoa in varicocele patients exhibited apoptotic features, whereas the rate was only 0.1% in healthy controls (36). These findings demonstrate that apoptosis is increased not only in testicular tissue but also in mature spermatozoa, confirming the continuity of the process.

Current literature shows that varicocele markedly enhances pathological apoptosis through mechanisms such as testicular heat elevation, hormonal imbalance, and oxidative stress. This increase in apoptotic activity compromises germinal epithelium integrity and leads to quantitative and qualitative loss of spermatozoa, providing a critical biological basis for infertility pathogenesis. Therefore, apoptosis should be considered not merely a consequence of varicocele-associated infertility but also a fundamental cellular response that drives the process forward and structurally weakens spermatogenesis.

1.3. Disruption of Endocrine Regulation in Varicocele

The hypothesis regarding decreased serum testosterone levels in infertile men with varicocele is based on the pathophysiological assumption that varicocele adversely affects Leydig cell function (37, 38). Leydig cells are responsible for androgen synthesis, which is critical for spermatogenesis, and are highly sensitive to varicocele-induced microenvironmental changes, including increased testicular temperature, oxidative stress, and venous stasis. Therefore, varicocele is thought to impair enzymatic processes involved in steroidogenesis and intracellular signaling pathways, leading to reduced testosterone biosynthesis.

In a large-scale multicenter study by the World Health Organization (WHO), the effects of varicocele on hormonal parameters were evaluated, and it was found that free testosterone levels in individuals over 30 years of age with varicocele were significantly lower compared to those under 30 (39). This finding suggests that the negative impact of varicocele on testicular endocrine function becomes more pronounced with increasing age. Age-related increases in hormonal sensitivity may be explained by the accumulation of oxidative stress in testicular

tissue, decreased Leydig cell reserve, and limited cellular regenerative capacity.

Studies by Cayan et al. investigating the effects of microsurgical varicocelectomy on hormonal profiles support these results (40). Measurable increases in testosterone levels after surgery suggest that varicocele indeed suppresses Leydig cell function and that surgical correction can improve testicular endocrine response. This indicates that microsurgical varicocelectomy may positively influence not only semen parameters but also hormonal balance.

However, a substantial number of studies report that hormone levels, including testosterone, FSH, LH, and estradiol, often remain within normal reference ranges in men with varicocele (41-44). These findings indicate that the hormonal effects of varicocele are heterogeneous and do not manifest uniformly across all patients. Factors influencing the occurrence of hormonal changes include varicocele severity, duration, patient age, concomitant testicular pathologies, lifestyle factors, and genetic predisposition.

Although there is no consensus in the literature regarding the effects of varicocele on hormonal regulation, current evidence suggests that varicocele can exert suppressive effects on Leydig cell function and testosterone production. Nonetheless, the fact that hormonal parameters are not impaired in all patients indicates that varicocele's impact on the endocrine system is patient-specific, multifactorial, and variable. Therefore, hormonal assessment in men with varicocele should not be considered a standalone diagnostic criterion but should be integrated with clinical findings, semen analysis, and physical examination for a comprehensive evaluation.

1.4. Epigenetic Modifications and Function of the Ubiquitin–Proteasome System (UPS)

The proper regulation of epigenetic mechanisms during spermatogenesis is crucial not only for ensuring adequate sperm function but also for the healthy progression of early embryonic development. Literature clearly demonstrates that the epigenetic environment of male gametes plays a significant role in establishing epigenetic marks in the embryo post-fertilization (45).

Consequently, epigenetic dysregulation in spermatogenesis not only limits male fertility but can also profoundly affect embryonic development, potentially leading to transgenerational biological consequences. Varicocele is a complex pathophysiological condition shaped by genetic, epigenetic, and environmental interactions. Epigenetic modifications—including DNA methylation, histone alterations, and RNA-based modifications such as N6-methyladenosine (m6A)—regulate genome activity independently of DNA sequence, potentially contributing to the development and clinical severity of varicocele. Recent studies have demonstrated disrupted sperm DNA methylation profiles in individuals with varicocele, while abnormalities in m6A-RNA methylation lead to functional impairments in critical gene expression steps (46). These epigenetic defects affect chromatin structure, DNA repair capacity, and transcriptional stability of spermatogenic cells, thereby reducing sperm quality and functionality.

The phenotypic variability of varicocele is influenced not only by genetic and epigenetic factors but also by environmental triggers such as heat stress, oxidative stress, and hypoxia (47, 48). Epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling, regulatory roles of noncoding RNAs, and RNA methylation. Certain modifications in germ cells, according to current evidence, can be transmitted intergenerationally, potentially leading to phenotypic changes in subsequent generations (49, 50). Over 100 chemical modifications have been identified on mRNA, tRNA, rRNA, and snRNA, among which m6A is the predominant epigenetic mark in mammalian mRNA, playing a critical role in transcriptional efficiency, mRNA stability, and translational control (51–55).

Disruptions in epigenetic regulation in varicocele patients are associated with impaired spermatogenesis and fertility loss. In particular, DNA methylation abnormalities and m6A-RNA modification changes correlate with increased DNA damage in high-grade varicocele, leading to significant functional sperm deficits (56). These findings suggest that varicocele is not solely a mechanical or hemodynamic disorder but also encompasses an epigenetic-based pathological phenomenon.

The ubiquitin–proteasome system (UPS) is a fundamental proteostatic mechanism involved in critical intracellular processes, including antigen

presentation, cell cycle control, apoptosis regulation, cellular defense responses, signal transduction, and transcription (57,58). Recent evidence indicates that UPS also plays essential roles in the male reproductive system, particularly during fertilization stages such as capacitation, acrosomal reaction, and zona pellucida binding. Ubiquitin, the core component of UPS, covalently tags substrate proteins, directing them to the 26S proteasome complex for degradation (59). The 26S proteasome consists of a 20S catalytic core and a 19S regulatory cap, with many 19S subunits exhibiting ATPase activity critical for proper recognition, unfolding, and degradation of proteins.

Ubiquitination occurs in three steps through the sequential action of E1 ubiquitin-activating, E2 ubiquitin-conjugating, and E3 ubiquitin ligase enzymes. This complex post-translational modification regulates protein degradation timing, cellular localization, and functional state. The 26S proteasome plays a central role in removing misfolded or damaged proteins during spermatogenesis, maintaining cellular protein homeostasis, and facilitating structural remodeling during sperm maturation. It also contributes to functional processes, including acrosomal reaction, sperm motility, and fertilization capacity. In varicocele, increased oxidative stress and testicular microenvironmental disruption reduce the expression and activity of proteasome subunits, impairing UPS function. This leads to the accumulation of damaged proteins, disrupted spermatogenesis, and compromised sperm function, highlighting a key molecular basis of varicocele-associated infertility. Recent studies indicate that the 26S proteasome is particularly active during capacitation, the process by which sperm acquire the ability to bind the oocyte and achieve fertilization (57).

Epigenetic regulatory mechanisms and the UPS increasingly represent critical molecular processes in varicocele pathophysiology. Varicocele alters the sperm epigenetic profile through disruptions in DNA and RNA methylation, histone modifications, and chromatin remodeling, while simultaneously affecting protein homeostasis via the UPS, leading to functional impairments during critical stages of spermatogenesis. When considered together, dysfunctions in these two systems demonstrate that varicocele is not merely a vascular pathology but a complex infertility condition shaped by the interplay of multilayered epigenetic and proteostatic mechanisms. Therefore, integrating epigenetic and UPS-based approaches in the study of varicocele-associated infertility holds substantial potential for developing more targeted diagnostic and therapeutic strategies.

2. Effects of Varicocele on Testicular Histology

At the macroscopic level, varicocele leads to a significant reduction in testicular volume, depending on disease stage and duration of exposure, with advanced cases resulting in true testicular atrophy characterized by progressive volume loss (60). In adults, left-sided varicocele is particularly associated with contralateral testicular volume loss (17). However, there is no distinctive histopathological feature that definitively differentiates varicocele from other testicular pathologies; as noted in existing studies, the observed changes are similar to those in cases with low spermatogenesis without varicocele and exhibit considerable variability (61).

Histopathologically, testes with varicocele show increased Leydig cell numbers, reduced Sertoli cell counts per seminiferous tubule, and prominent vacuolization in Sertoli cell endoplasmic reticulum (62). These alterations lead to germinal epithelium shedding, arrested maturation of spermatogenic cells, and thickening of the seminiferous tubule basal membrane (63). Bilateral testicular biopsies in men with left-sided varicocele have demonstrated similar histological features and Johnsen scores in both testes, suggesting that left-sided varicocele can exert contralateral effects and may involve additional underlying pathological mechanisms affecting the entire seminiferous tissue (64).

Spermatozoa frequently exhibit acrosomal developmental defects, cellular immaturity, and amorphous head anomalies (65). Cytoplasmic droplets retained in sperm are correlated with DNA damage and reactive oxygen species (66). As varicocele severity increases, thickening of the spermatic vein wall and increased smooth muscle content are observed. One study reported that in men with varicocele, while the venous lumen expanded, smooth muscle fibers and

vessel wall thickness increased, and a new longitudinal muscle layer formed in addition to the normally circular layer (67).

Electron microscopy and immunohistochemistry studies have revealed marked peritubular lamina propria sclerosis with decreased laminin and type IV collagen expression (68,69). Ultrastructural assessments of the blood–testis barrier indicate that Sertoli–Sertoli junction complexes are largely preserved and maintain basal compartment integrity, corroborated by functional data in animal models (70,71). Nevertheless, selective structural disruptions in Sertoli–Sertoli junctions and peritubular basal lamina in areas with germ cell loss indicate that testicular damage in varicocele is heterogeneous and progressive (72).

Spermatogenic cells exhibit various ultrastructural abnormalities, including abnormal chromatin distribution in spermatids, cytoplasmic vacuoles, membranous bodies, and acrosomal irregularities, with binucleated spermatids frequently reported (73). In adult varicocele, thickening of the lamina propria due to increased extracellular elements and deep invaginations toward the germinal epithelium have been repeatedly observed (69,73,74). In some patients, myoid cells retain normal ultrastructure but are embedded in an expanded extracellular matrix, occasionally showing membrane irregularities and reduced cytoplasmic extensions (75). Decreased myofibroblasts and increased fibroblasts have been confirmed by desmin and vimentin immunostaining (69).

Collectively, these findings demonstrate that varicocele induces multilayered and progressive structural alterations in testicular tissue. Cellular and extracellular changes significantly affect spermatogenesis and testicular function. The impact of varicocele is not confined to the affected testis but may indirectly influence the contralateral testis, suggesting that the condition may progress through systemic or microenvironmental pathological mechanisms. Therefore, varicocele should be considered a multifaceted testicular pathology, both morphologically and functionally, and early diagnosis with effective management is critical to reducing infertility risk.

Findings of the Review

Current literature indicates that varicocele is a complex pathology leading to progressive and multifaceted damage within the testicular microenvironment. Clinical and experimental studies have demonstrated that varicocele is associated with impaired sperm parameters, testicular volume loss, and reduced Leydig cell function. These effects are thought to result from the combined influence of increased oxidative stress, mitochondrial dysfunction, enhanced apoptosis, hormonal alterations, and disruption of protein homeostasis mediated by the ubiquitin–proteasome system (UPS). The interplay of these molecular processes supports the notion that varicocele is not merely a vascular disorder but a significant systemic cause of male infertility.

Studies show that varicocele induces a marked oxidative stress state characterized by elevated reactive oxygen species and reduced antioxidant defense capacity in testicular tissue. Increased oxidative burden is closely linked to sperm membrane lipid peroxidation, DNA damage, and impaired motility. Disruptions in the mitochondrial electron transport chain and reduced ATP production negatively affect sperm function as well as germ cell viability, highlighting oxidative stress and mitochondrial dysfunction as core molecular contributors to varicocele-associated infertility.

Evidence also indicates that varicocele is associated with increased apoptotic cell death in the testes, adversely affecting spermatogenesis. Oxidative stress, intratesticular hyperthermia, and hormonal disturbances are primary triggers of mitochondria-mediated apoptotic pathways. Elevated germ cell apoptosis in seminiferous tubules correlates with reductions in sperm count and quality, suggesting that apoptosis functions both as a marker and as a driver of varicocele-related testicular damage.

While the impact of varicocele on testicular endocrine function is variable, data suggest inhibitory effects on Leydig cell activity and testosterone production. Some clinical studies report decreased serum testosterone in affected individuals, with postoperative increases following varicocelectomy indicating partial reversibility. The heterogeneity of hormonal changes implies that endocrine disruption plays

a complementary role in varicocele pathophysiology.

Recent findings reveal that varicocele significantly affects epigenetic regulation of gene expression and protein homeostasis through UPS modulation. Disruptions in epigenetic marks, coupled with UPS suppression under elevated cellular stress, contribute to the accumulation of damaged proteins. Although data on direct UPS involvement in varicocele are limited, current evidence suggests that UPS dysfunction may represent a potential molecular mechanism underlying varicocele-associated infertility.

Histopathological analyses show seminiferous tubule degeneration, germ cell loss, basal membrane thickening, and structural alterations in Sertoli and Leydig cells. Ultrastructural studies reveal compromised blood–testis barrier integrity and increased extracellular matrix deposition. These morphological changes support the concept of varicocele as a multilayered pathology impacting both testicular architecture and functional integrity.

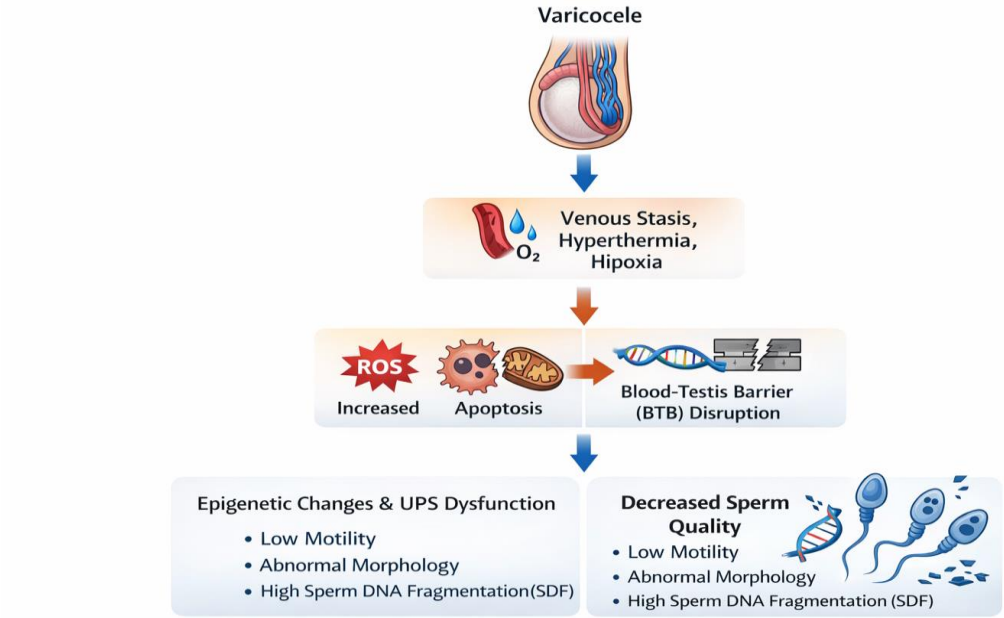

Figure 1. Mechanisms linking varicocele and infertility

Discussion

Varicocele represents a complex pathophysiological process in the testis, characterized not only by venous dilation but also by progressive and multifaceted cellular deterioration. Current literature demonstrates that varicocele weakens the microscopic architecture, intercellular communication, and metabolic integrity of the testis over time. Local hyperthermia and increased oxidative stress resulting from impaired venous return lead to significant mitochondrial dysfunction, thereby threatening the continuity of spermatogenesis. This stressed microenvironment has been associated with germ cell loss, disruption of cellular maturation processes, and insufficiency of testicular protective mechanisms. These findings underscore the importance of early diagnosis of varicocele and suggest that dysfunction of the ubiquitin–proteasome system (UPS) may serve as an early indicator of testicular damage and a potential molecular biomarker; however, studies directly evaluating the varicocele UPS relationship, particularly pre- and post-surgical dynamics, remain limited, highlighting a significant knowledge gap in this area.

Histopathological analyses identify seminiferous tubule degeneration, thinning

of the germinal epithelium, compromised Sertoli cell integrity, basal membrane thickening, and interstitial fibrosis as hallmark morphological features of varicocele. Structural damage to Sertoli cells is thought to increase blood–testis barrier permeability, negatively affecting germ cell protection and epigenetic stability of spermatogenesis. Furthermore, reduced Leydig cell density leads to decreased testosterone synthesis, disrupting intratesticular hormonal balance and the biochemical integrity of the tubular microenvironment, thereby exerting secondary adverse effects on spermatogenesis. These findings indicate that varicocele is a systemic testicular pathology affecting both anatomical and endocrine functions.

Recent studies on UPS have revealed that varicocele may also exert significant disruptive effects on cellular protein turnover. Accumulation of misfolded proteins under oxidative stress can overwhelm UPS regulatory capacity, resulting in disrupted protein homeostasis, increased germ cell apoptosis, and impaired protein transformation required for spermatid maturation. These processes, together with identified disruptions in sperm epigenetics, DNA packaging, and protamination, are believed to contribute to a multifactorial decline in sperm quality.

The data reviewed herein suggest that varicocele-induced infertility cannot be attributed to a single biological axis; rather, a complex pathophysiological network exists in which cellular stress responses, hormonal imbalances, epigenetic reprogramming, and disrupted protein homeostasis act simultaneously. Notably, alterations in DNA methylation, histone modifications, m6A-RNA marks, and UPS dysfunction have emerged as central molecular components of varicocele pathophysiology. Changes in DNA methylation and RNA modifications impact key cellular pathways involved in spermatogenesis, leading to disrupted gene expression and impaired germ cell development. Epigenetic alterations affecting DNA repair compromise genomic stability and sperm DNA integrity, while disruptions in chromatin organization adversely affect nuclear sperm structure and reduce fertilization potential.

The molecular and cellular mechanisms discussed in this review highlight varicocele's potential as a guiding factor in clinical management, beyond its descriptive role. Early molecular alterations, including oxidative stress, epigenetic changes, and UPS dysfunction, indicate that testicular damage may commence before clinical manifestations, emphasizing the importance of timely patient monitoring. Clinically, the distinction between adolescent and adult varicocele should be reconsidered in light of these mechanisms. While semen parameters in adolescents often provide limited information, early indicators at the molecular and cellular level may help identify at-risk individuals. In adults, integrating varicocele grade, semen parameters, and fertility history with biomarkers such as oxidative stress levels, epigenetic profiles, and UPS components may allow for a more comprehensive and informed clinical decision-making process.

Table 1. Molecular Mechanisms Associated with Varicocele

Mechanism	Biomarker / Measurement	Sample Type	Associated Clinical Outcome
Oxidative Stress	Reactive oxygen species (ROS), malondialdehyde (MDA), total antioxidant capacity (TAC)	Seminal plasma	DNA damage, reduced sperm motility
Mitochondrial Dysfunction	Mitochondrial membrane potential (MMP) loss	Spermatozoa	Decreased ATP production, reduced sperm motility

Apoptosis	Caspase-3 activation, Annexin V positivity	Testicular tissue / Sperm	Reduced sperm count
DNA Fragmentation	DNA fragmentation index (DFI) assessed by TUNEL or SCSA	Semen	Infertility, increased miscarriage risk
Epigenetic Alterations	Global or gene-specific DNA methylation levels	Spermatozoa	Impaired embryo development

The effectiveness of surgical intervention (varicocelectomy) and medical approaches is directly related to these molecular mechanisms. Increasing evidence suggests that post-surgical reduction in oxidative stress and partial restoration of cellular homeostasis is possible; however, the dynamics of epigenetic modifications and UPS function before and after surgery remain insufficiently elucidated. This highlights the need for reliable molecular markers capable of predicting treatment response (Table 1).

Therefore, varicocele management should adopt an integrated decision-making model that considers not only clinical staging and semen analysis but also patient age, disease severity, fertility expectations, and underlying molecular mechanisms. In this context, tables systematically correlating clinical parameters with molecular biomarkers can provide a practical and guiding tool for both clinicians and researchers.

In conclusion, varicocele is a multifactorial and progressive pathology that leads to extensive disruption of cellular organization, hormonal balance, and proteostatic mechanisms. Future studies should focus on thoroughly elucidating the relationships between oxidative stress and mitochondrial function, structural and functional changes in the UPS, and their impact on sperm epigenetics. A comprehensive understanding of these mechanisms will contribute to the prevention of varicocele-associated infertility and the development of more targeted therapeutic strategies.

Conclusion and Limitations of the Review

This narrative review comprehensively addressed the molecular and cellular pathophysiology of varicocele, evaluating the mechanisms underlying oxidative stress, mitochondrial dysfunction, the ubiquitin–proteasome system (UPS), and epigenetic alterations. However, due to its narrative design, the data could not be synthesized systematically or quantitatively, precluding the possibility of a meta-analysis. The heterogeneity of studies in the literatureincluding variations in study design, patient populations, and methodologies—limits the generalizability of the findings. Potential publication bias should also be considered, as the tendency to report positive outcomes may lead to the underrepresentation of negative or neutral results.

Furthermore, studies directly investigating the relationship between UPS and varicocele are limited, and data on the dynamics of epigenetic changes before and after surgical intervention remain insufficient, hindering the clinical translation of molecular biomarkers. Most available literature focuses on adult patients, with a notable lack of systematic studies evaluating early molecular alterations in adolescent varicocele. Future research should adopt a comprehensive approach to the oxidative stress–mitochondrial dysfunction–UPS–epigenetic axis of varicocele and prospectively monitor molecular changes before and after surgery. Such investigations would provide valuable insights for predicting treatment response and enabling personalized clinical management. In particular, the identification of early biomarkers in adolescents could facilitate the development of preventive strategies aimed at reducing infertility risk. Multi-center studies with standardized methodologies are warranted to clarify the molecular basis of varicocele-associated infertility and to facilitate the translation of these findings into clinical practice.

Declarations

Ethical Approval Certificate

Ethics committee approval is not required for this review article as it does not involve human or animal subjects.

Author Contributions Statement

All stages of the study, including the conceptualization, design, literature review, analysis, interpretation, writing, and critical revision, were entirely performed by SO.

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The author declares that this study received no financial support.

Conflict of Interest

The author declares no conflicts of interest

Declaration on the Use of AI

During the preparation of this manuscript, the author utilized generative AI tools to enhance linguistic clarity, grammar, and readability. These tools were also employed in the creation of figures and diagrams.

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