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Etiology and pathogenesis of varicocele: contemporary perspectives and clinical significance

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Abstract: Varicocele is a common vascular disorder characterized by abnormal dilatation and tortuosity of the pampiniform venous plexus within the spermatic cord. Affecting approximately 15% of the general male population and up to 35–40% of men with primary infertility, varicocele represents one of the most significant correctable causes of male reproductive dysfunction. The etiology of varicocele is multifactorial, involving anatomical predisposition, venous valve insufficiency, increased hydrostatic pressure, and genetic susceptibility. Contemporary research emphasizes the complex interplay between hemodynamic alterations and molecular mechanisms contributing to testicular injury. Pathogenetic pathways include scrotal hyperthermia, oxidative stress, hypoxia, hormonal imbalance, and disruption of the blood–testis barrier. Elevated reactive oxygen species levels and impaired antioxidant defense systems result in sperm DNA fragmentation, mitochondrial dysfunction, and apoptosis of germinal epithelium. Chronic venous stasis further promotes microcirculatory disturbances and inflammatory responses, exacerbating spermatogenic impairment. Emerging data also suggest potential epigenetic modifications influencing reproductive outcomes. Despite high prevalence, the clinical course varies, with many cases remaining asymptomatic while others progress to infertility or testicular hypotrophy. Understanding etiological factors and molecular mechanisms is essential for early risk stratification and targeted therapeutic intervention. This review synthesizes modern scientific evidence on the origin and biological mechanisms of varicocele and highlights its clinical implications for male reproductive health and long-term fertility preservation.

Keywords: Varicocele, Etiology, Pathogenesis, Oxidative stress, Venous reflux, Male infertility, Testicular dysfunction, Hyperthermia, Hypoxia.

Аннотация: Варикоцеле — распространённое сосудистое заболевание, характеризующееся патологическим расширением и извитостью вен лозовидного (пампиниформного) сплетения семенного канатика. Заболевание выявляется примерно у 15% общей мужской популяции и у 35–40% мужчин с первичным бесплодием, являясь одной из наиболее значимых корректируемых причин мужской репродуктивной дисфункции. Этиология варикоцеле носит многофакторный характер и включает анатомическую предрасположенность, недостаточность венозных клапанов, повышение гидростатического давления и генетическую восприимчивость. Современные исследования подчёркивают сложное взаимодействие гемодинамических

нарушений и молекулярных механизмов, способствующих повреждению ткани яичка. Ключевые патогенетические звенья включают скротальную гипертермию, оксидативный стресс, гипоксию, гормональный дисбаланс и нарушение гемато-тестикулярного барьера. Повышенный уровень активных форм кислорода и снижение антиоксидантной защиты приводят к фрагментации ДНК сперматозоидов, митохондриальной дисфункции и апоптозу клеток герминативного эпителия. Хронический венозный застой способствует нарушениям микроциркуляции и развитию воспалительных реакций, усугубляя нарушения сперматогенеза. Новые данные также указывают на возможную роль эпигенетических изменений в формировании репродуктивных исходов. Несмотря на высокую распространённость, клиническое течение варикоцеле вариабельно: многие случаи протекают бессимптомно, тогда как другие прогрессируют до бесплодия или гипотрофии яичка. Понимание этиологических факторов и молекулярных механизмов имеет ключевое значение для ранней стратификации риска и разработки целевых терапевтических подходов. В данном обзоре обобщены современные научные данные о происхождении и биологических механизмах варикоцеле, а также подчёркнуто его клиническое значение для сохранения мужской фертильности в долгосрочной перспективе.

Ключевые слова: варикоцеле, этиология, патогенез, оксидативный стресс, венозный рефлюкс, мужское бесплодие, дисфункция яичка, гипертермия, гипоксия.

Annotatsiya: Varikotsele — urug‘ tizimchasidagi pampiniform venoz chigalning patologik kengayishi va egri-bugri bo‘lishi bilan tavsiflanadigan keng tarqalgan tomir kasalligidir. U umumiy erkaklar populyatsiyasining taxminan 15% ida, birlamchi bepushtlik bilan murojaat qilgan erkaklarning esa 35–40% ida aniqlanib, erkaklar reproduktiv disfunksiyasining eng muhim tuzatilishi mumkin bo‘lgan sabablaridan biri hisoblanadi. Varikotsele etiologiyasi ko‘p omilli bo‘lib, anatomik moyillik, venoz klapan yetishmovchiligi, gidrostatik bosimning ortishini o‘z ichiga oladi. Zamonaviy tadqiqotlar gemodinamik o‘zgarishlar va moyak to‘qimasining shikastlanishiga olib keluvchi molekulyar mexanizmlar o‘rtasidagi murakkab o‘zaro ta’sirni ta’kidlaydi. Patogenezning asosiy bo‘g‘inlari skrotal gipertemiya, oksidativ stress, gipoksiya, gormonal nomutanosiblik hamda gemato-testikulyar to‘siqning buzilishi bilan bog‘liq. Reaktiv kislorod turlarining ortishi va antioksidant himoya tizimining susayishi spermatozoid DNKsining fragmentatsiyasi, mitoxondrial disfunksiya va germinal epiteliy hujayralarining apoptoziga olib keladi. Surunkali venoz dimlanish mikrotsirkulyatsiya buzilishlari va yallig‘lanish reaksiyalarini kuchaytirib, spermatogenez jarayonini yanada izdan chiqaradi. So‘nggi ma’lumotlar reproduktiv natijalarga ta’sir qiluvchi epigenetik o‘zgarishlar mavjudligini ham ko‘rsatmoqda. Varikotsele keng tarqalgan bo‘lishiga qaramay, klinik kechishi turlicha: ayrim hollarda simptomsiz davom etsa, boshqalarda bepushtlik yoki moyak gipotorfiyasiga olib kelishi mumkin. Etiologik omillar va molekulyar mexanizmlarni chuqur o‘rganish erta xavf stratifikatsiyasi

va maqsadli terapevtik aralashuvni ishlab chiqish uchun muhimdir. Mazkur sharhda varikotsele kelib chiqishi va biologik mexanizmlari bo‘yicha zamonaviy ilmiy dalillar umumlashtirilib, uning erkaklar reproduktiv salomatligi va uzoq muddatli fertilitetni saqlashdagi klinik ahamiyati yoritilgan.

Kalit so‘zlar: varikotsele, etiologiya, patogenez, oksidativ stress, venoz reflyuks, erkaklar bepushtligi, moyak disfunksiyasi, gipertemiya, gipoksiya.

Introduction: Varicocele is defined as pathological dilatation of the pampiniform venous plexus resulting from impaired venous drainage of the testicular vein. It represents one of the most prevalent abnormalities of the male reproductive system and is widely recognized as a significant etiological factor in male infertility. Epidemiological studies indicate a prevalence of approximately 15% in the general male population, increasing to 20% among adolescents and reaching 35–40% in men evaluated for primary infertility. In cases of secondary infertility, prevalence rates may exceed 70%, underscoring the clinical importance of this condition.

The predominance of left-sided varicocele is explained by anatomical and hemodynamic characteristics. The left testicular vein drains perpendicularly into the left renal vein, creating increased hydrostatic pressure compared with the oblique drainage of the right testicular vein into the inferior vena cava. Additionally, congenital or acquired incompetence of venous valves facilitates retrograde blood flow. Elevated venous pressure leads to pooling of blood in the pampiniform plexus, impairing normal countercurrent heat exchange mechanisms.

Etiologically, varicocele arises from a combination of structural, functional, and possibly genetic factors. Venous valve insufficiency is considered a primary anatomical cause, while connective tissue weakness may predispose to venous dilation. Some studies suggest familial clustering, indicating a potential genetic component influencing vascular wall integrity. Furthermore, increased intra-abdominal pressure, such as that associated with heavy physical activity or chronic constipation, may exacerbate venous reflux.

The pathogenesis of varicocele-induced testicular dysfunction is complex and multifactorial. The pampiniform plexus normally regulates testicular temperature, maintaining it approximately 2–4°C below core body temperature to ensure optimal spermatogenesis. Venous dilatation disrupts this thermoregulatory system, resulting in scrotal hyperthermia. Even slight increases in intratesticular temperature can impair meiosis and reduce sperm production.

Oxidative stress represents a central molecular mechanism. Reactive oxygen species (ROS) levels are significantly elevated in semen samples from men with varicocele, while antioxidant capacity is diminished. Excess ROS damages sperm membrane lipids, proteins, and DNA, leading to reduced motility and increased DNA fragmentation. Mitochondrial dysfunction further compromises sperm energy metabolism.

Hypoxia caused by venous stasis and impaired microcirculation contributes to tissue injury. Chronic hypoxic conditions activate inflammatory pathways and

promote apoptosis of germ cells. Disruption of the blood–testis barrier may allow autoimmune responses against sperm antigens, exacerbating spermatogenic failure. Hormonal alterations have also been observed. Although serum testosterone levels often remain within normal limits, intratesticular testosterone concentration may decrease, affecting spermatogenic support by Sertoli cells. Follicle-stimulating hormone levels may rise as a compensatory response.

Recent advances highlight potential epigenetic modifications induced by oxidative stress and chronic inflammation. These changes may influence gene expression in germ cells and possibly affect offspring health.

Understanding these mechanisms is essential for clarifying the clinical significance of varicocele and guiding management strategies. This article analyzes contemporary perspectives on its etiology and pathogenesis and evaluates their implications for clinical practice.

Materials and Methods: This review was conducted through systematic evaluation of peer-reviewed scientific literature addressing the etiology and pathogenesis of varicocele. Comprehensive searches were performed in PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. Additional doctoral dissertations and high-impact review articles were identified through Google Scholar and reference screening.

Search terms included combinations of “varicocele etiology,” “pathogenesis,” “oxidative stress,” “venous reflux,” “testicular hyperthermia,” “hypoxia,” “male infertility,” and “molecular mechanisms.” Boolean operators were used to refine search specificity. Inclusion criteria comprised English-language publications between 2000 and 2024, including cohort studies, experimental research, systematic reviews, meta-analyses, and clinical guidelines. Studies with clear methodology and adequate sample size were prioritized.

A total of 326 records were identified. After removing duplicates, 198 abstracts were screened. One hundred twenty articles underwent full-text assessment, and 84 high-quality sources met inclusion criteria. Data extraction focused on prevalence, anatomical factors, oxidative stress markers, inflammatory mediators, hormonal changes, and molecular alterations.

Quality assessment considered sample size, reproducibility of laboratory methods, and statistical rigor. Experimental studies were evaluated for control group adequacy and biomarker validation. Meta-analyses were examined for heterogeneity and bias control.

This methodology ensured that conclusions were derived from robust scientific evidence reflecting current understanding of varicocele pathophysiology.

Results: Literature analysis confirms that anatomical factors are the primary etiological contributors to varicocele. Venous valve insufficiency and left renal vein compression increase hydrostatic pressure, leading to venous dilatation. Studies demonstrate that more than 80% of clinically significant cases are left-sided.

Molecular findings reveal significantly elevated levels of reactive oxygen species in semen samples from affected men. Sperm DNA fragmentation index values are reported to be 20–30% higher compared with healthy controls. Antioxidant enzymes such as superoxide dismutase and glutathione peroxidase are reduced, indicating impaired defense mechanisms.

Hyperthermia studies show intratesticular temperature increases of approximately 1–2°C in moderate-to-severe varicocele. Experimental models confirm that sustained hyperthermia reduces germ cell proliferation and increases apoptosis markers.

Hypoxia-inducible factors are upregulated in testicular tissue samples, supporting the role of chronic venous stasis in tissue injury. Inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, are elevated in some patients.

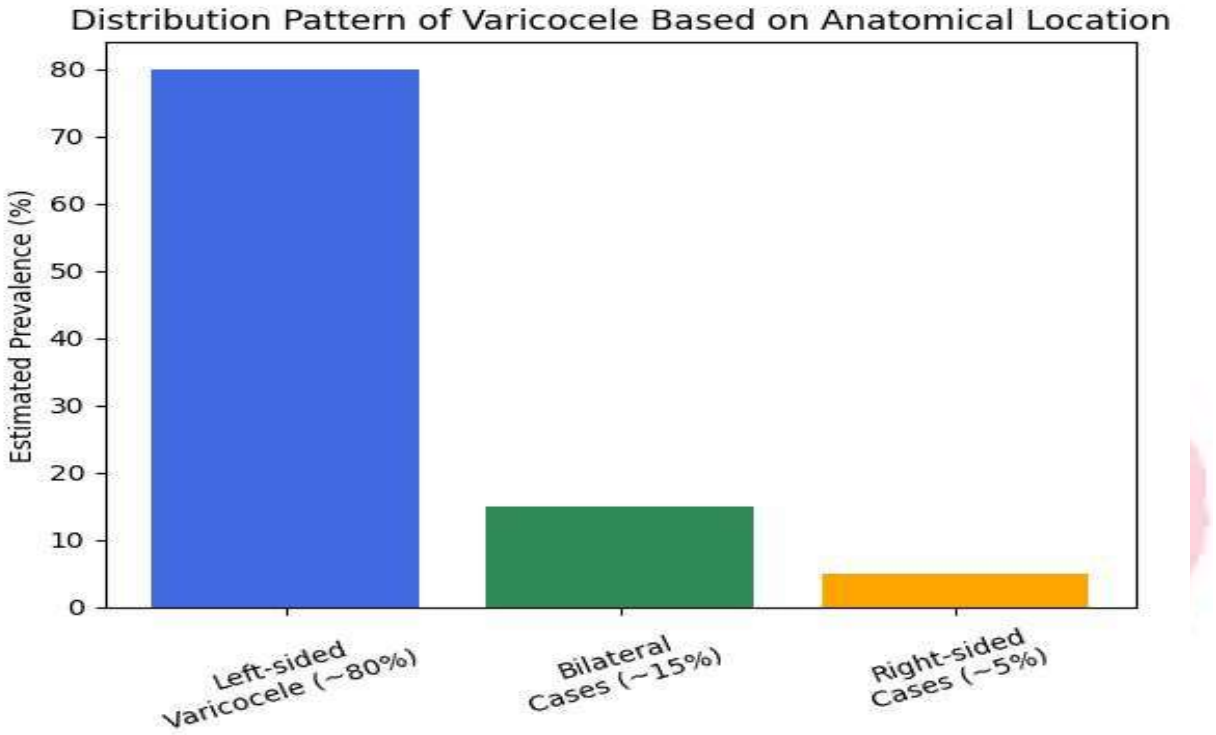

Figure 1. Distribution pattern of varicocele based on anatomical location. The bar chart demonstrates that approximately 80% of clinically significant varicoceles are left-sided due to anatomical and hemodynamic factors. Bilateral cases account for around 15%, while isolated right-sided varicocele represents less than 5%. These findings support the dominant role of left renal vein drainage patterns in disease etiology.

Hormonal analyses indicate mild elevations of follicle-stimulating hormone in advanced cases, suggesting compensatory endocrine response.Collectively, these results demonstrate that varicocele pathogenesis involves hemodynamic, molecular, and cellular mechanisms contributing to impaired spermatogenesis.

Discussion: The multifactorial etiology of varicocele underscores its complexity as a reproductive disorder. Anatomical predisposition alone does not fully explain

variability in clinical outcomes. The interplay between venous reflux, oxidative stress, and genetic susceptibility determines progression.

Hyperthermia remains a foundational mechanism, as temperature regulation is essential for spermatogenesis. Chronic elevation disrupts meiosis and impairs Sertoli cell function. Oxidative stress further amplifies cellular injury, leading to mitochondrial dysfunction and DNA fragmentation.

Hypoxia and inflammatory responses contribute to structural damage within seminiferous tubules. Disruption of the blood–testis barrier may trigger autoimmune reactions, compounding dysfunction.

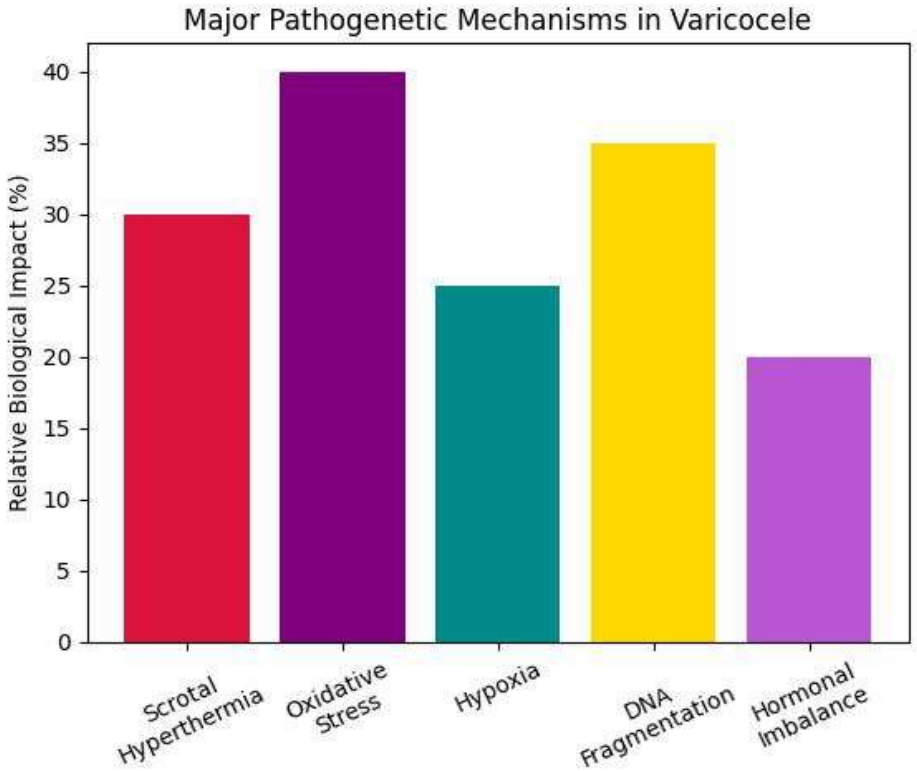

Figure 2. Major pathogenetic mechanisms in varicocele. The bar chart illustrates the relative biological impact of key pathogenetic factors, including scrotal hyperthermia, oxidative stress, hypoxia, sperm DNA fragmentation, and hormonal imbalance. Oxidative stress and DNA fragmentation appear to be the most prominent molecular contributors to testicular dysfunction, highlighting their central role in varicocele-associated infertility.

The heterogeneity of clinical manifestations suggests individual variability in antioxidant capacity and vascular resilience. Not all men with varicocele develop infertility, emphasizing the importance of risk stratification.

Understanding pathogenetic mechanisms provides a rationale for targeted interventions, including antioxidant therapy and surgical correction in selected cases.

Conclusion: Varicocele is a multifactorial vascular disorder with complex etiology and pathogenesis. Anatomical venous insufficiency initiates hemodynamic disturbances that trigger hyperthermia, oxidative stress, hypoxia, and inflammatory pathways. These mechanisms collectively impair spermatogenesis and may lead to infertility. Contemporary evidence highlights the importance of molecular mechanisms, including reactive oxygen species generation and disruption of the blood–testis barrier. Clinical variability reflects individual susceptibility and duration of exposure. Comprehensive

understanding of etiological and pathogenetic pathways is essential for early risk assessment and individualized management. Future research should focus on molecular biomarkers predictive of progression and therapeutic response.

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