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Precision Oncology

Review

Androgen deprivation therapy for prostate cancer: from mechanism of action, complications and challenges to future prospects

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ABSTRACT

Prostate cancer ranks among the most prevalent malignancies in men, with disease progression driven by sustained androgen receptor (AR) signaling. Androgen deprivation therapy (ADT), which suppresses androgen synthesis and AR activation, serves as the standard treatment for advanced disease. ADT modalities include surgical castration, gonadotropin-releasing hormone agonists/antagonists, anti-androgens, and androgen synthesis inhibitors. Despite initial efficacy, long-term ADT is frequently complicated by the emergence of castration-resistant prostate cancer (CRPC) and multi-system toxicities involving metabolic, cardiovascular, and skeletal systems. CRPC arises from AR reactivation via gene amplification, mutation, splice variants and crosstalk with oncogenic pathways. Contemporary treatment intensification combines ADT with next-generation AR inhibitors, chemotherapy, and immunotherapy. Predictive biomarkers such as AR variant 7 and homeobox B13 facilitate patient stratification and individualized treatment decisions. The aim of this review is to summarize the role of ADT in prostate cancer management, with particular emphasis on androgen metabolism, AR signaling, mechanisms of castration resistance, ADT-related complications, and emerging therapeutic strategies. Based on systematic literature retrieval from PubMed and Embase (2018–2025), this review synthesizes current knowledge on androgen metabolism, AR signaling, CRPC mechanisms, ADT-related complications, and emerging therapeutic strategies to optimize long-term outcomes.

Key Words: castration-resistant prostate cancer; androgen receptor signaling; treatment complications; precision oncology; predictive biomarkers

MeSH terms:

PROSTATIC NEOPLASMS, CASTRATION-RESISTANT — DIAGNOSIS

PROSTATIC NEOPLASMS, CASTRATION-RESISTANT — PHYSIOPATHOLOGY

PROSTATIC NEOPLASMS, CASTRATION-RESISTANT — THERAPY

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Introduction

Prostate cancer (PC) is the most prevalent malignancy in the male urogenital system, ranking the second most common cancer globally and the fifth leading cause of cancer-related deaths [1]. In 2022, it was estimated to have over 1.46 million new cases and more than 396,000 deaths [2]. This significant increase compared with historical incidence and mortality rates is driven by global demographic shifts, including an ageing population and rising life expectancy, particularly in lower- and middle-income countries. In addition to racial characteristics, risk factors for developing PC include genetic predisposition, chronic inflammation in prostate tissue known as prostatitis, environmental, professional and dietary factors, including high fat diet, smoking and excessive alcohol intake [3]. For clinically localized PC, radical prostatectomy and radiation therapy are standard, with adverse effects including incontinence and erectile dysfunction [4]. Active surveillance is an option for low-risk disease to avoid overtreatment [5]. For locally advanced disease, adding long-term androgen deprivation therapy (ADT) to local treatment improves outcomes, with chemotherapy added in high-risk cases [6]. ADT is standard for metastatic disease and is used as neoadjuvant approach in high-risk localized disease [7, 8]. Having outlined PC staging and treatment strategies, understanding its pathogenesis is key to optimizing ADT. PC development involves complex genetic, epigenetic, and metabolic alterations, with androgen signaling as a central driver.

The novelty of this study lies in the systematic integration of PC pathogenesis, androgen signaling, ADT mechanisms, castration resistance, and ADT-related multi-system complications. Rather than focusing on single therapeutic strategies or separate molecular mechanisms, this paper bridges the gap between basic hormone regulation and the clinical application of different ADT regimens, while also addressing long-term adverse reactions and tumor drug resistance. It is important to note that the presented logic linking fundamental research and clinical practice allows us to focus attention on the frequently encountered problems of long-term anti-androgen therapy.

The aim of this review is to summarize the role of ADT in PC, address its associated complications and resistance mechanisms, and provide an updated overview integrated with recent clinical evidence and international guidelines. A literature search was performed in PubMed and Embase from 2018 to 2025 using key terms including “castration-resistant prostate cancer”, “androgen receptor signaling”, “treatment complications”, “precision oncology”, and “predictive biomarkers”. Where necessary to clarify specific aspects of the publications under review, earlier studies were also considered. Only clinical trials, high-quality reviews, and mechanistic studies in English were included, except for selected Russian- and Chinese-language sources used in specific cases, while case reports were used selectively when relevant to rare complications or unusual clinical scenarios. The following section focuses on how dysregulated androgen metabolism and receptor signaling contribute to tumor initiation and progression.

Prostate cancer pathogenesis androgen signaling and molecular pathology

The clinical classification and corresponding treatment strategies for prostate cancer are summarized in Table 1. The pathogenesis of PC is complex and involves a combination of lifestyle factors, genetic mutations and epigenetic changes [9, 10]. These factors, including diet and obesity, can interact with inherited genetic predispositions in epithelial cells and lead to the disease development [11, 12]. Common genetic alterations in PC include androgen receptor (AR) amplification/mutation, phosphatase and tensin homolog (PTEN) loss (which activates the prosurvival phosphoinositide 3-kinase / protein kinase B / mechanistic target of rapamycin [PI3K/AKT/mTOR] pathway), and *MYC* overexpression driving uncontrolled proliferation and genomic instability [10, 13]. A recent study by Boufaied N. et al. shows that obesity, coupled with a diet high in saturated fats can initiate PC with *c-MYC* gene amplification [14].

Table 1. Clinical classification and corresponding treatment strategies for prostate cancer

Cancer staging	Core treatment principles	Key treatment approaches	Therapeutic goal
Clinically localized prostate cancer	Radical cure	Radical surgery (prostatectomy), radical radiation therapy, low-risk individuals can be actively monitored	Complete tumor removal and cure
Locally advanced prostate cancer	Primary and adjuvant	Radical surgery, radiotherapy, plus long-term androgen ADT (or combined with chemotherapy)	Reduce the risk of recurrence and prolong the disease-free survival
Metastatic prostate cancer	Control, survival	ADT, second-generation anti-androgens, chemotherapy, targeted, and immunotherapy	Delay progression, relieve symptoms, prolong survival

Note: ADT — androgen deprivation therapy.

PC belongs to hormone-sensitive tumors, as cancer cell proliferation is initially dependent on external signals in the form of androgens [15]. During normal prostate development, the AR is highly expressed in stromal cells and absent in epithelial cells. However, as PC progresses, stromal AR expression declines but epithelial AR becomes dominant [16]. While androgens normally regulate prostate cell growth via AR, PC is driven by aberrations in androgen biosynthesis, metabolism, and AR function, which promote tumor progression and castration resistance. Understanding these alterations is therefore essential for elucidating disease mechanisms and advancing targeted therapies.

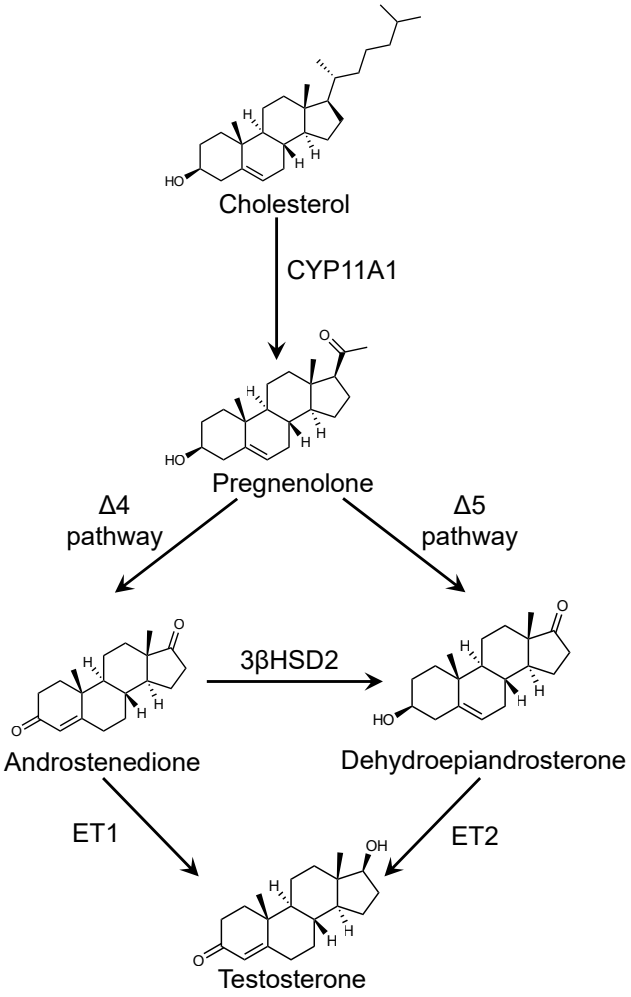
Androgen synthesis and metabolism

Androgen synthesis and metabolism maintain normal prostate physiology. In PC, these pathways are often dysregulated and reprogrammed, promoting tumor progression and ADT resistance. A clear understanding of these processes is critical to revealing how cancer cells reshape the androgen microenvironment to evade treatment.

Androgens in the human body are primarily synthesized in the testicular interstitial cells of males and the ovarian and adrenal cortex of females. The core androgen biosynthetic pathway begins with cholesterol, which is catalyzed by cholesterol side-chain cleavage enzyme (CYP11A1) to form pregnenolone [17]. This pregnenolone then undergoes two intermediate pathways — Δ5 and Δ4 — yielding dehydroepiandrosterone (DHEA) and androstenedione, respectively.

After several enzymatic reactions DHEA and androstenedione are eventually converted to testosterone [18] (Figure 1).

FIG. 1. Androgen synthesis pathway

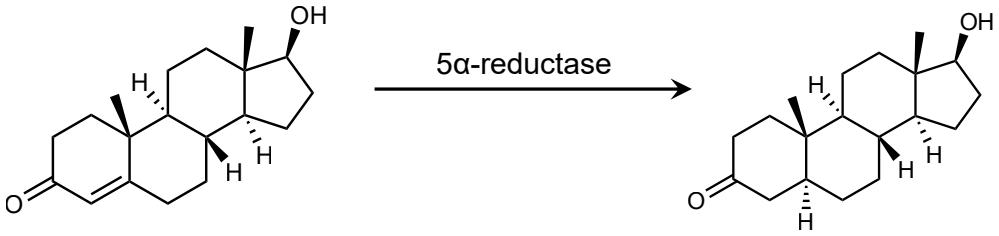


Note: CYP11A1 — cytochrome P450 family 11 subfamily A member 1; 3βHSD2 — 3β-hydroxysteroid dehydrogenase type 2; ET1 — several enzymatic reactions required for androstenedione to get converted into testosterone; ET2 — several enzymatic reactions required for dehydroepiandrosterone to get converted into testosterone.

Androgens in the human body are metabolized by enzymes in the liver and peripheral tissues. As the most abundant cytochrome P450 (CYP) enzyme in the liver, CYP3A4 is responsible for the metabolism of numerous exogenous substances and the synthesis and transformation of endogenous substances [19]. For androgens, the CYP family primarily employs CYP3A4 and CYP2C9/19. The former mainly catalyzes hydroxylation reactions of androgens such as testosterone, converting testosterone into 6β-hydroxytestosterone while participating in reduction and hydrolysis processes. The latter assists in the oxidative metabolism of androgens, serving as a compensatory mechanism when CYP3A4 activity is limited to ensure complete metabolic processes [20].

In peripheral tissues, androgens are either converted into the more active dihydrotestosterone form or locally inactivated, achieving tissue specificity [21]. The primary enzyme involved in the conversion (Figure 2) is 5α-reductase (5AR), which has two subtypes in humans: 5AR1 and 5AR2. The former is mainly distributed in the skin [22], while the latter exhibits higher activity in the prostate and visceral fat, responsible for converting testosterone into dihydrotestosterone (DHT).

FIG. 2. Peripheral metabolism of androgens



Testosterone Dihydrotestosterone

Recent studies indicate that gut microbiota metabolize conjugated hormones into free DHT via β-glucuronidase [23]. The concentration of DHT in feces can be over 70 times higher than in serum, creating a unique high-DHT microenvironment, which provides an additional source of androgens for PC lesions [23]. More importantly, after ADT, the DHT synthesis involving gut microbiota remains unaffected. This may allow DHT to reach PC through bloodstream, thereby promoting tumor growth. Meanwhile, the high DHT microenvironment can disrupt microbial balance, triggering chronic inflammation that further accelerates tumor progression [24].

Structural and functional aberrations of the androgen receptor

Central to the PC pathophysiology is the AR, a nuclear receptor that mediates the biological effects of androgens, primarily testosterone and DHT. AR is a modular protein composed of several distinct structural domains that play crucial roles in its function. N-terminal domain (NTD) is responsible for transcriptional activation by binding to co-activators, such as p160 family, to initiate downstream gene expression [25]. NTD contains activation function (AF)-1, a modular region with key transcriptional activating units 1 and 5, which work in cooperation with AF-2 of the ligand-binding domain (LBD) for full gene activation, controlling downstream protein interactions and signaling [26]. The C-terminal LBD, responsible for binding with androgens, undergoes conformational changes, presents AF-2 at the surface to interact with coactivators, which further stabilizes the AR-DNA complex to promote transcription initiation [27]. The DNA binding domain recognizes and binds to androgen response elements (ARE) on target genes via a conserved zinc finger structure [28]. Each of these domains contributes to AR's ability to regulate gene expression in response to hormonal signals, highlighting its role as a key player in PC biology.

In PC cells, abnormal activation of AR involves both traditional DNA-binding actions and rapid non-genomic signaling interaction with PI3K/AKT/mTOR and mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) pathways, thereby driving continuous cell division, preventing cell death, and maintaining tumor growth [29, 30]. The traditional activation of AR signaling pathway involves ligand binding, conformational activation and associated release of heat shock proteins, leading to AR nuclear translocation, where it forms a dimer and binds to ARE to initiate transcription [31]. In treatment-naïve locally advanced PC, AR acts as a master regulator of the G1-S phase transition increasing the activity of cyclin-dependent kinases, phosphorylating retinoblastoma protein to release early region 2 binding factor, and reducing the cell cycle inhibitor p27, which ultimately promotes

DNA replication and cell proliferation [32]. Apart from this mechanism central to PC progression, the transcriptional activity of AR could be also modulated via coregulators that do not bind to DNA but enhance or repress transcription via chromatin remodeling [33, 34]. Among all AR coregulators, Forkhead box protein A1 is a crucial pioneer acting as a gatekeeper that binds to condensed chromatin, remodels nucleosomes to create accessible sites for AR binding, thereby controlling hormone-driven gene expression of PC [35].

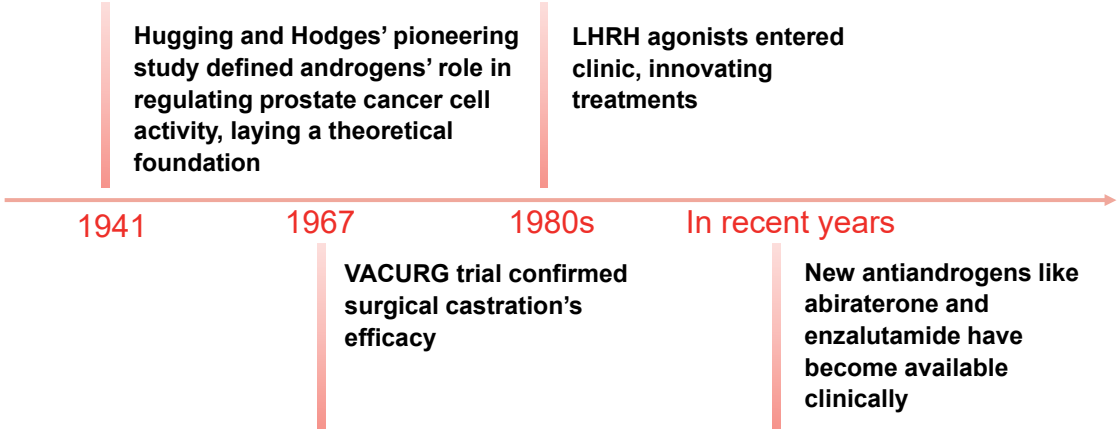
The complexity of AR signaling is further underscored by the existence of AR splice variants (AR-V) and AR gene amplification, that are significant players in PC progression and therapy resistance apart from the canonical full-length AR [36]. AR-V7 lacks the C-terminal LBD of the full-length receptor and functions as a constitutively active, ligand-independent transcription factor that stimulates tumor growth [37]. Additionally, missense mutations in the AR gene can alter ligand affinity and cause agonist-like activity by changing the shape of the LBD, particularly helix 12, allowing the receptor to bind to anti-androgens and activate the AR pathway instead of blocking it [38]. The common mutations include H874Y, F876L, T877A, W741L/C [39] that are the key drivers of resistance to ADT and treatment failure. Collectively, all these factors function as crucial intermediaries that dictate the strength and outcome of AR signaling in PC progression.

Androgen deprivation therapy and castration resistance

Androgen deprivation therapy modalities and clinical application

In 1941, Charles Huggins and Clarence V. Hodges pioneered a groundbreaking study that has identified the effects of androgens on the activity of PC cells [40] (Figure 3). This discovery established the androgen-driven model for PC, using serum phosphatases as biomarkers of PC, and laid the foundation for hormonal therapy, for which Huggins received the Nobel Prize in 1966 [41].

FIG. 3. The development of androgen deprivation therapy



Note: LHRH — luteinizing hormone-releasing hormone; VACURG — Veterans Administration Cooperative Urological Research Group.

The rationale behind ADT is based on the dependence of PC cells on androgens, and when androgen stimulation is lost, AR signaling pathway is inactivated, resulting in the inhibition of tumor cell growth and proliferation [40]. This includes surgical castration (orchiectomy) or pharmacological castration with agents that suppress hormone production (gonadotropin-releasing

hormone (GnRH) agonists / antagonists, androgen synthesis inhibitors) or block AR (anti-androgens). The overall information about available ADT methods is summarized in Table 2.

Table 2. Comparison of androgen deprivation therapy methods

Treatment category	Representative drugs/methods	Pharmacological effects and mechanisms	Key clinical features*	Notes and limitations*
Surgical castration [42]	Orchiectomy	Directly remove testicular androgen source to rapidly lower testosterone.	Advantages: rapid onset (within 24 h), permanence, low cost, no medication adherence issues. Indications: patients needing rapid testosterone reduction with advanced diseases.	Irreversible, psychological impact, persistent somatic side effects (e.g., hot flashes, osteoporosis).
GnRH agonists [43]	Leuprorelin, goserelin, triptorelin	Stimulate pituitary GnRH receptors for desensitization, inhibiting LH/FSH secretion and reducing testosterone synthesis.	Features: presence of "flare-up phenomenon" (transient testosterone elevation in the initial 1–2 weeks). Dosing: 1/3/6/12-month formulations. Flare-up management: concurrent use of antiandrogens (e.g., bicalutamide) for 2–4 weeks with the first dose to block flare-up risk.	Mainstream ADT option, monitor cardiovascular risks and long-term bone loss.
GnRH antagonists [44]	Degarelix	Directly block pituitary GnRH receptors, rapidly inhibiting LH and FSH secretion without testosterone flare-up.	Features: faster onset, no "flare-up phenomenon". Dosing: Loading dose 240 mg, maintenance 80 mg/month. Comparison: Efficacy comparable to agonists, but injection site reactions are more common, and anaphylaxis risk requires attention.	Patients need immediate, rapid testosterone reduction and intolerant to flare-up risk.
Antiandrogens [45]	First-generation: flutamide, bicalutamide Second-generation: enzalutamide, apalutamide, darolutamide	Competitive AR blockade. First-generation: AR LBD targeting. Second-generation: LBD blockade and AR nuclear translocation inhibition.	Features: monotherapy preserves testosterone/sexual function but inferior to castration. Application: often combined with GnRH analogs (CAB). Combined therapy or intermittent ADT.	Enzalutamide (high BBB permeability; monitor fatigue/falls); darolutamide (low BBB permeability; fewer central side effects).
Androgen synthesis inhibitors [46, 47]	Abiraterone, ketoconazole	Irreversibly inhibit CYP17A1 enzyme, blocking androgen synthesis in testicles, adrenal glands, and tumors.	Feature: potent systemic androgen suppression. Dosing: concurrent use with prednisone (5 mg, twice daily) to prevent mineralocorticoid excess. Indication: metastatic CSPC, non-metastatic CRPC.	Ketoconazole (early agent) is largely replaced by abiraterone due to significant hepatotoxicity and modest efficacy.

Note: * — Unless otherwise cited, the content in these columns reflects the authors' interpretive summary of the literature and does not constitute verbatim statements from individual references; GnRH — gonadotropin-releasing hormone; LH — luteinizing hormone; FSH — follicle-stimulating hormone; ADT — androgen deprivation therapy; AR — androgen receptor; LBD — ligand-binding domain; CAB — combined androgen blockade; BBB — blood-brain barrier; CYP17A1 — cytochrome P450 family 17 subfamily A member 1; CSPC — castration-sensitive prostate cancer; CRPC — castration-resistant prostate cancer.

First-line options for ADT involve reducing testosterone levels through surgical castration or pharmacological castration with GnRH antagonists or GnRH agonists combined with anti-androgens [48]. Surgical castration, orchiectomy, involves the removal of one or both testicles, leading to a significant reduction in testosterone production. While testosterone level below 50 ng/dL has long defined as "castration" in PC treatment, clinical studies suggest that reaching testosterone levels below 20 ng/dL as a result of bilateral orchiectomy leads to more profound androgen suppression, delaying disease progression and improving biochemical relapse free survival of patients [49, 50]. Orchiectomy is particularly effective in advanced PC as it offers immediate hormonal control, providing a rapid relief for patients

with metastatic disease. However, this definitive treatment is associated with psychological impacts, loss of libido, infertility and erectile dysfunction [51]. GnRH agonists, such as leuprolide and goserelin, act by overstimulating the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [52]. This therapy initially causes a testosterone flare, with peak serum testosterone at days 2–3, returning to baseline by days 7–8. Sustained overstimulation downregulates pituitary GnRH receptors, leading to castration levels of testosterone by approximately 2–3 weeks [53]. This mechanism makes GnRH agonists effective in reducing androgen levels over time, but the initial flare can exacerbate bone pain and spinal cord compression in patients with metastatic disease, necessitating a concurrent administration of anti-androgens to block the action of testosterone during the first few weeks of treatment [54, 55]. This combined approach, termed maximal androgen blockade, manages the initial surge, though GnRH antagonists could offer rapid androgen deprivation without flare and microsurges. Unlike GnRH agonists, GnRH antagonists provide a distinct approach by competitively binding to GnRH receptors in the pituitary gland and decreasing LH and FSH secretion [56]. Degarelix, most common GnRH antagonist, provides a rapid disease control, resulting in castration levels of testosterone within the first 3 days of therapy [57]. This makes GnRH antagonists particularly advantageous for PC patients who may experience complications from testosterone flare during the initial treatment phase with leuprolide [58]. First-generation antiandrogens, flutamide and bicalutamide, are non-steroidal molecules that prevent androgen binding to AR, thereby competitively inhibiting AR in PC cells and leading to tumor regression [59]. These antiandrogens are often used in conjunction with castration therapies, GnRH agonists, to enhance therapeutic efficacy. However, prolonged treatment with flutamide or bicalutamide is associated with side effects and most importantly, can lead to the development of castration-resistance [60]. Notably, the clinical role of non-steroidal antiandrogens (NSAAs) remains controversial. According to the European Association of Urology (EAU) guidelines, combined androgen blockade using NSAAs confers only a small survival benefit (< 5%) compared with ADT monotherapy, and this modest advantage must be balanced against increased adverse events. Given the superior efficacy of newer combination regimens, NSAAs are generally recommended only when other standard combination therapies are not available [61, 62].

Castration-resistant prostate cancer: definition and resistance mechanisms

Castration-resistant prostate cancer (CRPC) develops after loss of sensitivity to the initial ADT. As a result, PC relapses as the hormone-refractory disease, in which tumor cells are able to survive and proliferate despite the castration levels of testosterone [63]. Clinical criteria for the CRPC diagnosis include biochemical relapse or radiographic progression, evidenced by newly formed metastatic lesions, that develop at the serum testosterone concentration maintained below 50 ng/dL. Biochemical progression involves three consecutive serum prostate-specific antigen (PSA) increases with each 50% higher than the previous lowest point, separated by at least one week, and a final PSA level exceeding 2.0 ng/mL [64]. In 90% of cases with metastatic CRPC, bone metastases are developed, reducing the median survival of patients to 1.5-2 years [65]. One of the key events driving CRPC involves reactivation of AR signaling, when PC cells acquire advantageous adaptations for overcoming ADT. The mechanisms of hormone-refractory PC

growth include amplification or mutation of the AR gene, alternative splicing of AR and formation of AR-V7, increased synthesis of endogenous androgens from cholesterol or progesterone, activation of AR by non-androgen ligands such as glucocorticoids and antiandrogens acting as agonists [66]. It has been shown that AR-V7-mediated castration resistance in PC is attributed to reactivation of genes involved in lipid biosynthesis with fatty acid synthase being associated with poor prognosis and disease relapse [67]. The principal metabolic difference between CRPC and androgen-sensitive tumors is enhanced *de novo* lipogenesis controlled by Sterol Regulatory Element-Binding Proteins (SREBP), which are transcription factors activating a number of genes involved in lipid biosynthesis [15]. SREBP-1, encoded by the *SREBF1* gene, is overexpressed in advanced stages of PC and in androgen-independent tumors [68]. Hyperexpression of the gene, encoding SREBP-2, was detected in tumor tissues of patients with metastatic cancer, and in *in vivo* model systems of CRPC, nuclear expression of this factor increases threefold compared to androgen-sensitive tumors [69]. There is evidence of increased activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the most important enzyme of the mevalonate pathway of sterol biosynthesis, in PC cells resistant to AR inhibitors [70]. Therapy resistance of PC could be also driven via alternative tumor activation pathways, when AR suppression triggers androgen-independent mechanisms. Several growth factors including insulin-like growth factor 1 and epidermal growth factor can activate tyrosine kinase Src or lipid kinase PI3K that directly phosphorylate tyrosine residues on the AR, thereby triggering ligand-independent activation of AR [71]. Another important mechanism underlying progression of CRPC involves overactivity of oncogenic signaling pathways MAPK and PI3K/AKT that switch cancer cells to alternative survival routes independently of AR [29]. Finally, the tumor microenvironment plays a significant role in the hormone-refractory prostate tumorigenesis and immunosupression. It was identified that under ADT, tumor-associated macrophages deliver cholesterol to PC cells, thereby stimulating the synthesis of endogenous androgens. This metabolic cooperation triggers AR signaling pathway and ultimately leads to the progression of CRPC [72].

In addition to dysregulated lipid metabolism, glucose metabolism and glycolytic reprogramming also play critical roles in PC progression. Increased expression of monocarboxylate transporters (MCT) 1 and 4 contributes to enhanced glycolysis and lactate export in tumor and stromal cells, and high stromal MCT4 expression is significantly associated with biochemical recurrence and poor prognosis in patients with aggressive PC [73]. MCT1 and MCT4 promote glycolytic reprogramming and malignant progression in PC by mediating lactate transport between tumor and stromal cells. Their overexpression is closely associated with poor patient prognosis, supporting the rationale for developing targeted therapies against metabolic pathways [74].

Contemporary treatment strategies for castration-resistant prostate cancer

For patients with CRPC, standard treatment consists of next-generation AR inhibitors, often combined with chemotherapy, targeted therapy, or immunotherapy to improve survival. Second-generation antiandrogens, enzalutamide and abiraterone, have been developed to overcome resistance mechanisms associated with first-line therapies [75]. Androgen synthesis inhibitors like abiraterone acetate target the enzymatic pathways involved in androgen production. By inhibiting CYP17A1 enzyme, abiraterone decreases the production of not only testosterone but also deplete residual non-gonadal

androgens [76]. This dual action is particularly beneficial for CRPC, in which cancer cells may adapt by utilizing alternative sources of androgens for growth. The use of abiraterone has been associated with significant improvements in overall survival when combined with prednisone, corticosteroid agonist [77]. The concurrent administration of abiraterone and glucocorticoids is standard to suppress the hypothalamic-pituitary-adrenal axis manage side effects such as hypokalemia, hypertension and fluid retention related to mineralocorticoid excess as a result of CYP17A1 inhibition [78]. Second-generation AR antagonists, enzalutamide, apalutamide and darolutamide, not only block the LBD of AR, but also inhibit its nuclear translocation, DNA binding and coactivator recruitment, leading to a more comprehensive blockade of androgen signaling [79]. Recent clinical trials in chemotherapy- and hormone-naïve metastatic PC show that enzalutamide or abiraterone, either used alone or in combination with ADT, could significantly improve metastasis-free and overall survival, suggesting the necessity to use these agents as the first-line options for high-risk advanced cases for better disease control and patient outcomes [80]. The landmark LATITUDE study proved that combining abiraterone with ADT significantly improves overall survival and radiographic progression-free survival in newly diagnosed high-risk metastatic castration-sensitive PC, reducing mortality by 38% [81]. Similarly, the ARCHES trial demonstrated long-term survival advantages for enzalutamide combined with ADT in metastatic hormone-sensitive PC, reinforcing the benefit of intensified AR pathway inhibition [82].

The clinical data presented in this section, including drug dosing, treatment regimens, and clinical recommendations, have been reviewed and aligned with the following international clinical practice guidelines: the EAU Guidelines on PC (2024 Update) [61], the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Prostate Cancer (Version 3.2026) [83], the European Society for Medical Oncology Clinical Practice Guidelines for Prostate Cancer (2020) [84], and the American Society of Clinical Oncology Guideline on Systemic Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer (2025 Update, Living Guideline Version 2026.1) [85, 86]. Where discrepancies between sources exist, the recommendations reflect the consensus across these major guideline bodies.

Common side effects and complications of androgen deprivation therapy and their management

According to clinical data, approximately 50% of PC patients receive ADT during their disease course [87]. However, long-term ADT causes significant adverse effects due to disrupted hormonal homeostasis, including sexual dysfunction, metabolic disorders, cardiovascular diseases, osteoporosis, and anemia, which severely impair quality of life and may become life-threatening in severe cases [88]. Notably, ADT-related complications are also pathophysiologically associated with tumor microenvironment remodeling and therapeutic resistance.

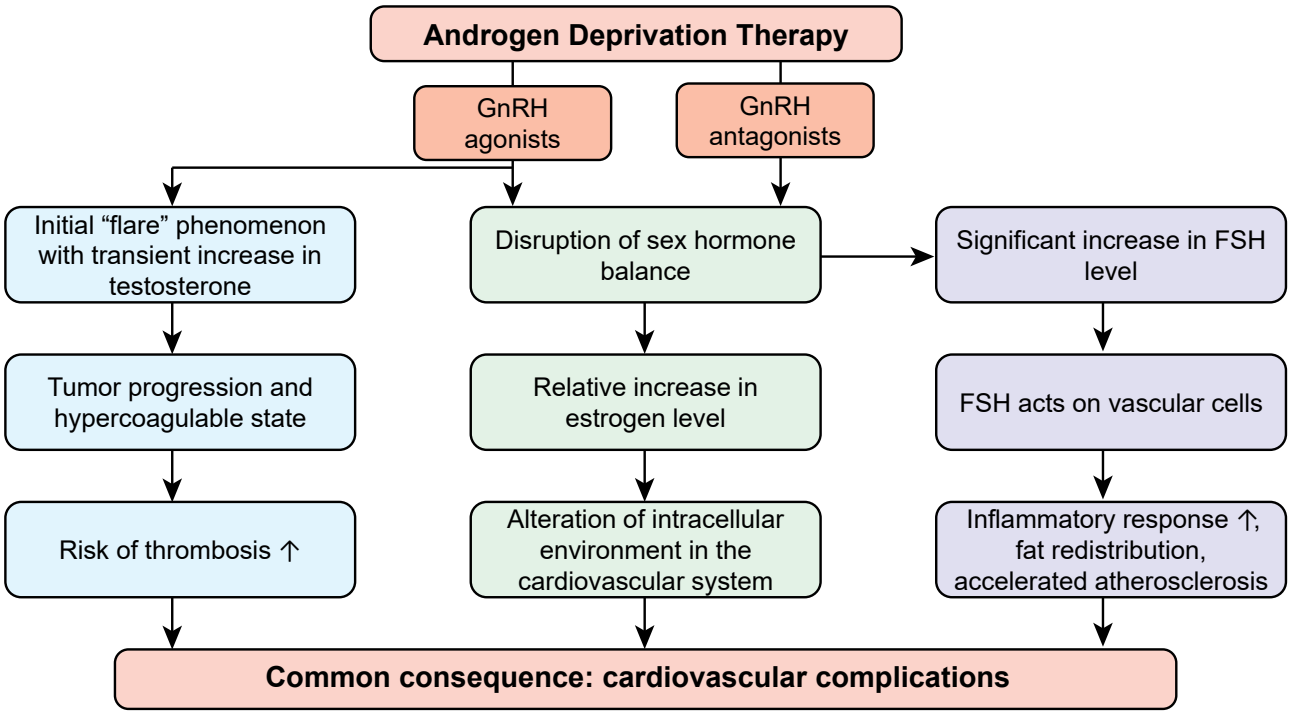
Cardiovascular diseases

According to prospective multicenter studies, PC patients receiving ADT increase the risk of developing major adverse cardiovascular events (MACE) [89]. A study in China showed that the overall prevalence of cardiovascular diseases in this group reached 27.0%, with 7.2% being multiple cardiovascular diseases. Additionally, the prevalence of hypertension was as high as 43.1%, and half of the patients had poor blood pressure control, further exacerbating their cardiovascular risks [90]. In PC patients with a history of heart failure,

myocardial infarction or arrhythmias, a risk of cardiovascular death during ADT treatment significantly increases [91].

FSH binds to its receptor on vascular endothelial cells and activates the PI3K/AKT/mTOR/NF-κB (Nuclear factor-κB) signaling cascade, which further upregulates the expression of vascular cell adhesion molecule-1 and E-selectin, thereby promoting endothelial inflammation and atherosclerosis [92]. As a result, this triggers inflammatory processes and accelerates the progression of atherosclerosis, thereby establishing a mechanism for plaque rupture and greater risk of cardiovascular diseases [93]. The disruption of hormonal homeostasis during ADT also contributes to hypercoagulable state and substantially increases the risk of thrombosis in PC patients [94]. Meanwhile, ADT-induced disruption of androgen–estrogen balance further alters the internal environment of cardiovascular system, becoming another significant factor affecting cardiovascular risk. These mechanisms collectively reveal the multifaceted pathophysiological basis of ADT's cardiovascular toxicity (Figure 4). Evidence from clinical trials suggests that GnRH antagonists exhibit significantly better cardiovascular safety than agonists [95]. Analysis of the side effects of GnRH agonists versus antagonists suggests that degarelix is associated with lower incidence of MACE, myocardial infarction and stroke compared to agonists, particularly for patients with pre-existing heart disease [96].

FIG. 4. Core diagram of mechanisms underlying cardiovascular complications associated with androgen deprivation therapy



Note: GnRH — gonadotropin-releasing hormone; FSH — follicle-stimulating hormone.

A systematic risk assessment strategy for ADT-induced cardiovascular complications involves thorough baseline cardiovascular evaluation and continuous monitoring during treatment [97]. In terms of intervention strategies, lifestyle modifications, including individualized dietary approaches for effective weight management, regular physical activity and smoking cessation, remain the cornerstone in mitigating ADT-induced adverse cardiovascular effects. At the pharmacological level, statins not only regulate blood lipids but may also

exert additional protective effects through the anti-inflammatory mechanisms. For PC patients with comorbid hypertension and diabetes, enhanced blood pressure and glucose control are both critical in cardiovascular prevention [98–100]. Optimal cancer treatment requires multidisciplinary collaboration between oncologists and cardiologists to balance antitumor efficacy and cardiovascular safety, defining cardio-oncology as a key component of modern comprehensive cancer care [101].

Metabolic syndrome and diabetes

AR signaling plays the critical role in metabolic homeostasis by enhancement of insulin sensitivity and direction of lipid metabolism in muscle tissues and liver, thereby preventing fat gain and promoting lean mass [102]. This is the reason why androgen deficiency under ADT is the key driver of metabolic syndrome and the progression to type 2 diabetes mellitus [103]. Clinical evidence suggests that ADT is significantly associated with dyslipidemia (total cholesterol increased by 7–10%, triglycerides by 26%), altered body composition (visceral fat accumulation with muscle loss), insulin resistance, and elevated fasting blood glucose levels [104]. These effects increase diabetes risk in PC on ADT, while also significantly raising the risk of liver pathology [105].

Sarcopenia and physical decline

The underlying mechanism of ADT-induced muscle loss, termed as sarcopenia, is associated with reduced androgen-supported muscle protein synthesis [106]. As a result, PC patients on ADT lose lean muscle mass while gaining fat mass, ultimately developing sarcopenic obesity, which increases risks for type 2 diabetes mellitus, MACE, bone fractures, and reduced physical function [107]. Clinical management for preserving muscle mass during ADT requires a multifaceted approach, which includes resistance-based exercises coupled with protein, vitamin D and calcium supplementation alongside monitoring mass changes [108, 109].

Osteoporosis and bone fracture risk

Androgens maintain bone metabolic balance through both direct effects, activation of osteoblast AR receptors, and indirect pathways, conversion into estrogen and muscle-skeletal coupling [106, 108, 110]. As a result of ADT, a significant loss of bone density develops in PC patients within the first 6–9 months of therapy [111]. After 2 years of ADT, 42.9% of men develop osteoporosis, and the proportion rises to 80.6% with ≥10 years of ADT, which features trabecular bone destruction and bone resorption greater than bone formation [112]. Therefore, bone-protective agents such as bisphosphonates, which trigger osteoclast apoptosis and denosumab, a monoclonal antibody against receptor activator of NF-$\varkappa$B ligand that prevents osteoclast formation, are used to improve bone mineral density in PC patients receiving long-term ADT.

Anemia

Physiologically, testosterone raises erythropoietin levels and stimulates erythropoiesis, promoting the differentiation of bone marrow haematopoietic stem cells into erythroid cells, a process disrupted by ADT [113]. ADT increases the risk of iron deficiency anemia in men with prostate cancer. The key underlying mechanism of this side effect involves ADT-induced testosterone deficiency that directly suppresses differentiation and proliferation of erythroid progenitor cells in the bone marrow [114]. The primary therapeutic interventions

aimed to mitigate the anemic syndrome in PC patients on ADT include nutritional support with iron, vitamin B_{12} and folate supplementation along with erythropoiesis-stimulating agents [115].

Sexual dysfunction

The primary cause of sexual dysfunction following ADT is the dramatic decline of testosterone that plays a critical role in maintaining libido and erectile function [116]. Although GnRH agonists may cause the initial testosterone surge, but eventually these pharmacological agents lead to castration levels of androgens via persistent suppression of pituitary function and GnRH receptor desensitization [43, 55]. AR is highly expressed in the smooth muscle cells of the corpus cavernosum. Physiologically, testosterone binding to AR activates nitric oxide (NO) synthase, which promotes NO production and smooth muscle relaxation in corpus cavernosum through the cGMP signaling pathway, thereby maintaining the erection [117]. ADT-associated testosterone deficiency reduces NO availability that impairs vasodilation and reduces penile blood flow, ultimately leading to erectile dysfunction [118]. Furthermore, decline of serum testosterone levels results in reduced stimulation of insula, frontal lobe and thalamus, brain regions involved in sexual desire [119]. This neurological shift serves as the explanation for ADT-associated decreased libido and sexual interest. Treatment typically involves sexual therapy and short-term ADT withdrawal for recovery.

Cognitive decline

Androgens exert crucial regulatory effects on key cognitive brain regions such as the hippocampus and prefrontal cortex through their AR [120]. These mechanisms primarily involve support of neuron survival in the hippocampus, promotion of long-term potentiation and dendritic spine growth, suppression of neuroinflammation. They also increase neprilysin, which is responsible for Aβ clearance and prevention of plaque buildup [121]. Clinical observations indicate that patients undergoing ADT develop widespread cognitive impairment after six months of treatment characterized by significant decline in multiple cognitive domains including attention, memory and executive functions [122]. From the perspective of pathophysiology, these cognitive impairments are closely related to the reduced neurogenesis, impaired synaptic plasticity, aggravated neuroinflammatory response and imbalance of neurotransmitter system, which need to be managed and treated in cooperation with neurologists and psychiatrists [123].

Future prospects

Therapeutic intensification

ADT remains a cornerstone of advanced PC management, with diverse strategies adapted to individual patient and disease characteristics. Since each approach has distinct benefits and drawbacks, treatment selection should account for tumor stage, patient preference, adverse effects, and progression risk [124]. Although ADT continues to be a foundational component in the treatment of metastatic PC, its limitations necessitate a shift towards combination therapies that leverage synergies with other treatment modalities, aiming to improve survival outcomes [125]. Recent evidence from ARASENS and PEACE-1 trials suggests that addition of docetaxel and second-generation antiandrogens to ADT, termed as triplet therapy, provides greater survival benefits for patients with metastatic castration-sensitive PC by intensifying

initial treatment beyond the ADT alone [126]. It has been shown that the triple therapy darolutamide + ADT + docetaxel reduces the risk of cancer-related mortality by 31% [127]. This treatment regimen has been recommended at the highest level (Grade I) in the Chinese Society of Clinical Oncology Prostate Cancer Diagnosis and Treatment Guidelines and has become an important clinical choice in oncological practice [128].

Immuno-metabolic synergy

The integration of immunotherapy approaches such as immune checkpoint blockade, adoptive cell therapy and tumor vaccines with ADT represents a promising avenue for enhancing treatment outcomes [129]. Immune checkpoint inhibitors have revolutionized the treatment of various malignancies, but their role in PC is still evolving with modest results as single agents but displaying durable responses in combinations with hormonal agents, chemotherapy or poly adenosine diphosphate ribose polymerase (PARP) inhibitors [130]. Preclinical mechanistic studies in PTEN-deficient PC models demonstrate that combining programmed cell death-1 (PD-1) inhibitors with ADT (degarelix) and pan-PI3K inhibition (copanlisib) significantly improves treatment response rates over single or dual therapies. Mechanistically, this triple combination upregulates major histocompatibility complex II on immunosuppressive PD-1^{hi} macrophages, enhances their phagocytic activity, remodels the tumor microenvironment, and boosts therapeutic efficacy [131]. Evidence suggests that ADT could increase the number of circulating naïve T cells, stimulate T-cell infiltration into the prostate tissue and decrease immune tolerance to PC cells, making it a rationale for combining androgen ablation with therapeutic vaccines for augmented effector T-cell responses [132, 133]. Furthermore, recent studies highlight the potential link between the gut microbiome and the efficacy of ADT. The composition of gut microbes may influence ADT response by modulating systemic immune status, offering new avenues for improving prognosis through microbial regulation [134]. Thus, the synergy between these immunotherapeutic approaches and ADT could potentially overcome therapy resistance in PC, resulting in durable responses and improved clinical outcomes of patients.

It is now becoming clear that treatment of advanced PC patients and the complications of ADT represents a serious economic and clinical challenge, requiring significant expenditure of the healthcare budget, particularly in patients with existing comorbidities [135, 136]. The existing interplay between AR signaling and aberrant lipid metabolism of PC suggests that reprogramming lipid uptake, synthesis and accumulation in cancer cells could enhance the efficacy of ADT while mitigating its adverse effects, including dyslipidemia and obesity [137]. Experimental studies have shown that ADT in combination with inhibitors of HMGCR, a key enzyme in the mevalonate pathway of sterol biosynthesis, significantly suppresses the growth of enzalutamide-resistant PC [70]. Clinical evidence that combination of HMGCR inhibitors, statins, with ADT mitigates cardiovascular risks associated with long-term hormonal therapy while potentially enhancing anti-tumor efficacy [138]. Pharmacological reprogramming of key metabolic rearrangements in PC could be potentially achieved by combination of ADT with SREBP inhibitors targeting *de novo* lipogenesis.

Innovative technology and support

In the context of advanced PC, drug repurposing offers a pragmatic approach to therapy discovery. It capitalizes on the known safety profiles of existing medications to provide new options for patients with limited choices [139].

For instance, thermoreversible self-assembling polymers can be completely dissolved at low temperature and then spontaneously assemble into uniform-sized nanovesicles, when the temperature rises to body temperature. This serves as the ideal platform for intelligent encapsulation and on-demand release of drugs, particularly into the most vulnerable cell populations responsible for PC metastasis and therapy resistance [140–142].

Finally, systemic support for PC patients on ADT, particularly those with comorbidities, remains equally vital. The supplements and natural products with pharmacological activity can mitigate ADT-induced side effects such as anemic or metabolic syndromes and improve overall nutritional status, thereby supporting overall health during long-term disease management [123].

With the emergence of next-generation hormonal agents, chemotherapy and immunotherapy, combination regimens have produced substantial gains in survival for PC patients with high-risk or metastatic disease, signaling a shift toward more intensive and biologically guided treatment paradigms. Looking ahead, advances in precision medicine, supported by genomic, molecular and metabolic profiling of PC patients are expected to refine the balance between efficacy and tolerability of the therapy. Deep understanding of the complex interplay between androgen signaling, metabolism and PC biology holds a significant potential for developing novel targeted approaches that can be effectively combined with ADT to overcome castration resistance.

Predictive biomarkers

This dual approach, which refers to blocking androgen dependence and disrupting the key metabolic support system of the tumor simultaneously, may achieve synergistic effects by blocking androgen dependence while disrupting key metabolic support system of the tumor [143]. Precision medicine in CRPC has been further advanced by the identification of key molecular markers and regulatory mechanisms. Among these, AR-V7 and homeobox B13 (HOXB13) have emerged as promising predictive biomarkers with potential to guide individualized treatment [144].

In the PROPHECY study of 118 metastatic CRPC patients, AR-V7 positivity was associated with significantly shorter progression-free and overall survival (adjusted hazard ratio 1.9–2.4 and 3.5–4.2, respectively), with PSA response rates of 0%–11% versus 26–28% in AR-V7-negative patients [145]. Moreover, AR-V7 detection is influenced by circulating tumor cell (CTC) burden: CTC-positive/AR-V7-positive samples exhibit higher CTC counts and tissue AR-V7 expression, yet discordance between CTC and tissue AR-V7 status is common: 63% of CTC-negative patients and 62% of CTC-positive/AR-V7-negative patients had detectable AR-V7 protein in matched biopsies [146].

HOXB13 is a lineage-specific transcription factor and AR coregulator consistently expressed across PC stages. It demonstrates high sensitivity (97%) and specificity (99%) for identifying prostate origin, outperforming conventional markers in advanced metastatic disease. Notably, HOXB13 remains detectable in 84% of AR-negative CRPC and neuroendocrine prostate cancer, supporting its utility as a diagnostic biomarker for confirming prostate lineage, particularly in challenging cases [147]. Furthermore, *HOXB13* abundance correlates with *PSMA* expression and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) standardized uptake values at both mRNA and protein levels, suggesting that PSMA PET may serve as an imaging biomarker reflecting HOXB13 transcriptional activity in aggressive disease [148].

Beyond AR-V7 and HOXB13, other predictive biomarkers have emerged in CRPC. Homologous recombination repair mutations (e.g., *BRCA2*) predict PARP inhibitor sensitivity [149, 150]. These biomarkers reflect the molecular heterogeneity of CRPC and highlight the value of comprehensive genomic profiling.

Conclusions

In summary, the treatment of PC has transitioned from simple androgen deprivation to a multimodal paradigm combining targeted, immunological, and metabolic approaches. This review focuses on mechanistic and pathophysiological insights relevant to ADT action, and associated adverse events. This review provides a comprehensive overview of key pathophysiological processes, although emerging targeted therapies, novel immunotherapies, or real-world evidence are not extensively covered owing to scope limitations; molecular biomarkers such as AR-V7 and HOXB13 are briefly introduced. Future progress requires a deeper understanding of the crosstalk between androgen signaling and the tumor microenvironment. By integrating ADT within precision-guided frameworks, we can optimize therapeutic efficacy, mitigate complications, and ultimately improve long-term patient outcomes.

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Translational Pathophysiology

Review

Therapeutic translation across myocardial infarction and myocardial contusion: opportunities, boundaries, and bidirectional lessons

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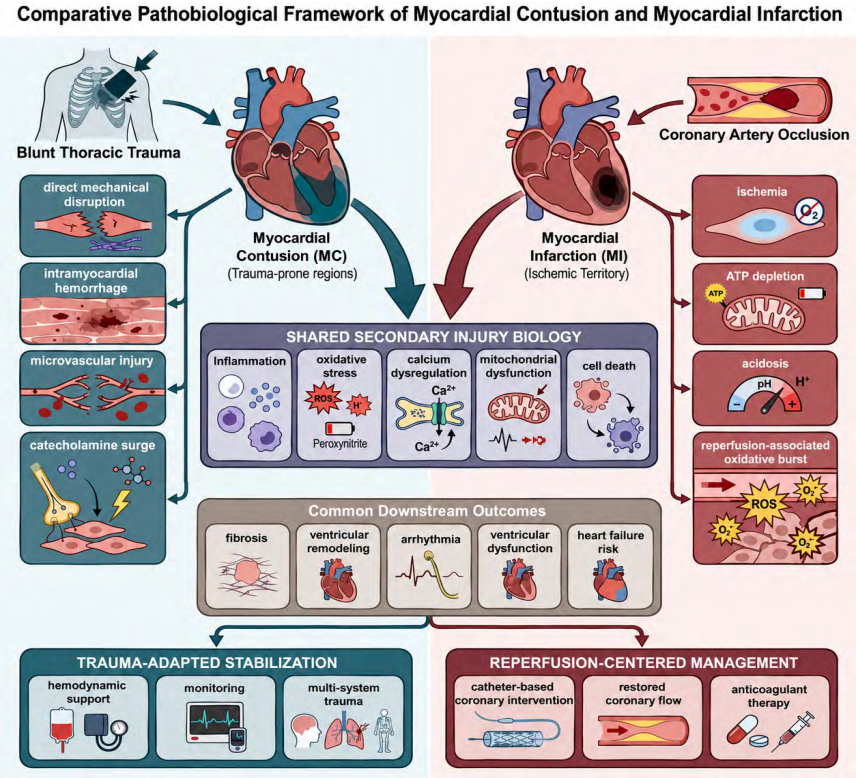
ABSTRACT

This review examines the asymmetric therapeutic relationship between myocardial contusion (MC) and myocardial infarction (MI). Although these two forms of myocardial injury arise from different initiating events, they converge across key secondary injury pathways, including inflammatory activation, oxidative stress, calcium dysregulation, cell death, fibrosis, and ventricular remodeling. Its aim is to clarify which elements of MI generate biologically portable hypotheses for MC, which remain clinically non-transferable, and how trauma reveals the contextual limits of canonical MI care. Evidence was retrieved from PubMed and CNKI primarily covering publications between January 2000 and January 2026 including experimental studies, clinical investigations, imaging studies, and guideline or consensus documents. The comparative literature indicates that the major divergence between MC and MI lies not in the mere presence of myocardial injury, but in the primary insult, the spatial organization of tissue damage, the logic of diagnostic interpretation, and the sequence of therapeutic decision-making. In this context, MI should be regarded not as a directly transferable treatment template for MC, but as a more mature source of mechanism-based hypotheses, particularly for the modulation of inflammatory amplification, oxidative injury, maladaptive remodeling, rhythm-risk surveillance, and biomarker-imaging integration. Conversely, MC is clinically informative less as a therapeutic analogue of MI than as a boundary condition that clarifies the dependence of myocardial injury management on etiology, bleeding risk, structural injury, and competing clinical priorities. Future research should prioritize trauma-specific phenotyping, multimodal diagnostic stratification, biomarker-imaging integration, and prospective evaluation of adjunctive targeted compatible with trauma care without delaying stabilization.

Graphical abstract



Key Words: blunt cardiac injury; ischemic myocardial injury; cardioprotection; biomarker-imaging integration; ventricular remodeling; rhythm-risk stratification; trauma-adapted management; translational pathobiology

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MYOCARDIAL INFARCTION — THERAPY
REVIEW
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Introduction

Myocardial contusion (MC) and myocardial infarction (MI) are usually discussed within separate clinical frameworks, yet comparison between them is increasingly valuable because the key question is no longer whether they look superficially similar, but how far therapeutic reasoning can travel across them. MC remains a diagnostically and clinically heterogeneous entity within blunt cardiac injury [1, 2], whereas MI is a more mature ischemic syndrome with clearer diagnostic and therapeutic architecture [3]. Their initiating insults are fundamentally different: mechanical trauma in MC and ischemia in MI, but both converge across several downstream pathways of myocardial injury. The relevance of this comparison is therefore therapeutic rather than merely descriptive: MI offers a disease model from which mechanism-based hypotheses may be drawn [4, 5], whereas MC clarifies why diagnostic and treatment algorithms cannot be transferred uncritically across etiologies [6].

Current work can be read through two complementary lenses. One emphasizes shared secondary injury biology, especially inflammation, oxidative stress, calcium dysregulation, mitochondrial dysfunction, and remodeling [7, 8]. The other emphasizes clinical non-equivalence, including differences in trigger, injury geometry, tempo, monitoring logic, and treatment priority [9, 10]. The mainstream view is not that one perspective displaces the other, but that biological overlap and clinical divergence must be interpreted together.

From a translational standpoint, this asymmetry is central. MI is managed through guideline-defined pathways organized around ischemic recognition, invasive evaluation, reperfusion or revascularization when indicated, antithrombotic therapy, and secondary prevention [9, 11]. Contemporary classification work and the universal definition further emphasize that MI is not a generic troponin-positive state but an ischemic syndrome requiring etiologic interpretation [12–14]. MC, by contrast, commonly arises in polytrauma, hemorrhagic shock, thoracic injury, and uncertain structural contexts. Its clinical pathway is therefore governed by stabilization, phenotyping, rhythm surveillance, and selective structural intervention rather than automatic entry into an acute coronary syndrome (ACS) algorithm [15–17].

Accordingly, this review examines MC and MI across four interrelated domains: initiating and secondary injury mechanisms, biomarkers and imaging, divergent clinical pathways, and therapeutic significance. Its aim is to clarify which elements of MI provide biologically portable hypotheses for MC,

which remain clinically non-transferable, and how the trauma setting exposes the contextual limits of canonical MI care. Literature searches were performed in PubMed and CNKI predominantly between January 2000 and January 2026 using key terms including “blunt cardiac injury”, “myocardial contusion”, “myocardial infarction”, “pathophysiological mechanisms”, “biomarkers”, “electrocardiographic and imaging findings”, “acute management”, “remodeling”, and “long-term outcomes”. Where necessary to clarify specific aspects of the publications under review, earlier studies were also considered. Only experimental models, clinical investigations, guidelines, and major reviews in English were included, while case reports were used selectively when relevant to rare complications or unusual clinical scenarios.

Shared pathobiological mechanisms

Primary insult and early secondary injury

The most fundamental difference between MC and MI lies in the initiating lesion. MC is trauma-driven and typically begins with direct mechanical disruption of cardiomyocytes, the microvasculature, and myocardial architecture. Depending on the force vector and site of impact, the resulting injury may include focal hemorrhage, edema, myofibrillar damage, and regional contractile dysfunction [3, 18], with the right ventricle often being particularly vulnerable because of its anterior position, with anteriorly located cardiac structures exposed to direct precordial force in some mechanisms [17, 18]. MI, by contrast, is ischemia-driven. Its primary lesion reflects abrupt and sustained impairment of coronary perfusion, most commonly due to acute atherothrombosis in type 1 MI, whereas acute infection and other systemic stressors can contribute to type 2 MI through oxygen supply-demand imbalance [19–21]. The current definitional literature further underlines that this ischemic setting is central to the meaning of infarction itself [13].

An additional temporal distinction is essential for therapeutic interpretation. In MI, particularly when the ischemic interval is limited, contractile dysfunction may precede irreversible cardiomyocyte death. This creates a clinically important window in which viable myocardium, postischemic stunning, and chronically dysfunctional hibernating myocardium may recover after timely reperfusion or revascularization [7, 8, 22]. Reperfusion remains indispensable for infarct-size limitation, but it may also intensify oxidative stress, calcium overload, inflammation, endothelial dysfunction, and microvascular impairment [7, 8]. MC follows a different sequence. Mechanical impact can produce immediate sarcolemmal disruption, myofibrillar damage, microvascular rupture, intramyocardial hemorrhage, and spatially irregular structural destruction before secondary inflammatory or metabolic amplification becomes clinically dominant [3, 18, 23]. Therefore, the reversible ischemic phenotypes of stunning and hibernation in MI should not be treated as direct analogues of primary traumatic tissue disruption in MC.

Despite this difference at onset, the early secondary injury response in the two conditions shows substantial convergence. Across both entities, the literature mainly centers on a common cluster of early disturbances: bioenergetic failure, impaired oxidative phosphorylation, intracellular acidosis, membrane instability, and calcium overload. In MC, these alterations are usually interpreted as consequences of tissue disruption, local hypoperfusion, trauma-related metabolic stress, and, in severe cases, post-traumatic cardiac dysfunction within shock physiology [23–25]. Severe blunt chest trauma studies also support an early metabolic and electrolyte component to this

injury environment [25]. In MI, the same downstream cascade is driven by ischemia and is often intensified during reperfusion [7, 8, 26].

A key conceptual point is that the overlap emerges downstream rather than upstream. The two diseases do not share a common trigger, but they do converge in the expansion phase of myocardial injury. This is precisely why comparison is biologically informative: it identifies a shared substrate of secondary damage without obscuring the fundamentally different nature of the primary insult.

Inflammation, oxidative stress, and calcium dysregulation

Among the shared mechanisms, inflammatory activation is one of the most consistently emphasized in literature. In MI, the dominant model describes a sequence in which necrotic cardiomyocytes release danger-associated signals, activate resident immune cells, recruit circulating leukocytes, and initiate a transition from injury amplification to repair [26–28]. In MC, the mechanistic literature is smaller and less standardized, but the prevailing view is that trauma likewise induces an acute inflammatory response characterized by oxidative imbalance, contractile impairment, and tissue-level repair signaling [24, 29, 30]. Experimental work further suggests trauma-associated shifts in structural and intercellular signaling that are compatible with this inflammatory phenotype [23, 30, 31].

Oxidative stress represents a second major area of convergence. Research in MI has moved from general recognition of reactive oxygen species injury toward a more detailed focus on mitochondrial dysfunction, reperfusion-associated oxidative burst, and redox-sensitive injury pathways [7, 32]. Lipid-lowering and plaque-oriented interventional studies remain important to MI care but should not be confused with generic transferability to traumatic injury [33]. In MC, the literature remains more limited, but current work broadly supports the view that oxidative injury arises from cellular disruption, inflammatory activation, mitochondrial damage, and depletion of endogenous antioxidant defenses [34, 35]. In this respect, the research trajectory has shifted from descriptive acknowledgment of post-traumatic injury toward more mechanism-based discussion of redox imbalance and metabolic vulnerability.

Calcium dysregulation can be regarded as a mechanistic bridge linking energetic failure, inflammation, and electrical instability. In both MC and MI, impaired production of adenosine triphosphate and membrane transport dysfunction favor intracellular calcium accumulation, with downstream effects on excitation-contraction coupling, protease activation, mitochondrial injury, and arrhythmogenic susceptibility [24, 25]. The immediate upstream drivers differ: trauma-related catecholamine excess may intensify calcium-mediated myocardial dysfunction after blunt chest trauma [25, 36, 37], whereas ischemia-reperfusion injury and sarcoplasmic reticulum-mitochondrial calcium signaling are more central in MI [7, 8]. The clinical relevance of this electrical vulnerability is underscored by the close relationship between ischemic injury and rhythm disturbance after MI [38].

Cell death, fibrosis, and remodeling

The major downstream consequence of these intersecting pathways is cardiomyocyte loss followed by structurally significant repair. In MC, experimental work has mainly focused on apoptosis-related signaling, caspase activation, and alterations in structural proteins involved in cytoskeletal integrity and intercellular coupling [30, 31]. In MI, literature is broader and more differentiated. This broader mechanistic literature is also supported by well-

established experimental models of MI and ischemia-reperfusion injury [39]. Beyond necrosis, current work increasingly emphasizes apoptosis, necroptosis, ferroptosis, and fibroblast-driven repair programs that shape infarct expansion and scar formation [26, 40, 41]. The inflammatory-remodeling literature also continues to support this broader reparative framework [27, 28].

Fibrosis and ventricular remodeling are also shared endpoints, but they follow different spatial and pathological logic. MI typically produces organized scar formation within a vascular territory and may drive remote ventricular remodeling, chamber dilation, and progressive systolic dysfunction [4, 42]. MC may show acute and late abnormalities visible on cardiac magnetic resonance imaging [43]. Emerging antifibrotic work underscores how central remodeling has become to post-MI therapeutic thinking [44]. MC more often produces focal, heterogeneous, and trauma-shaped repair that reflects injury geometry rather than coronary anatomy [45, 46]. Contemporary state-of-the-art reviews likewise emphasize the irregular, mechanically determined distribution of traumatic cardiac injury [47]. Thus, while both diseases can culminate in wall-motion abnormalities, arrhythmogenic substrate formation, and impaired ventricular reserve, the architecture of repair differs substantially.

Taken together, the literature supports a general framework in which the shared biology of MC and MI is concentrated in secondary injury and repair, whereas the most important differences lie in the origin, distribution, and clinical expression of that injury. This distinction is central to any meaningful comparison between the two conditions.

Divergent clinicopathological pathways

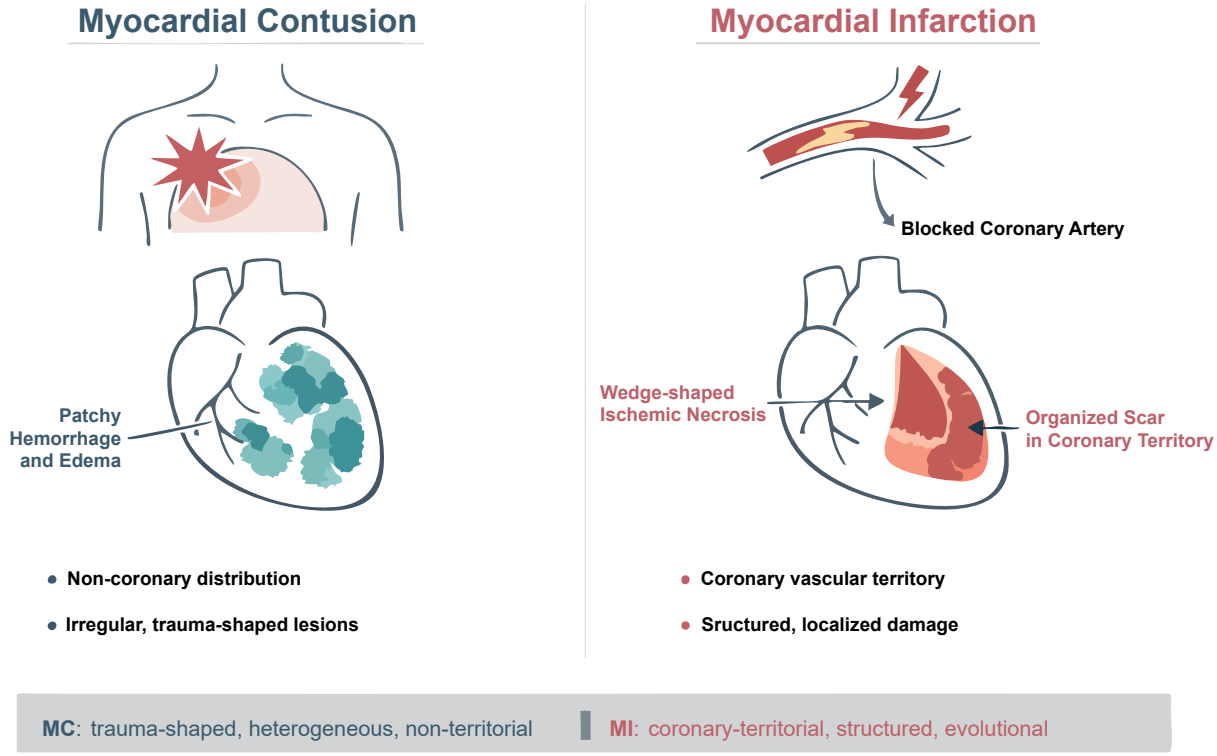
Morphology, injury distribution, and pathology

The most clinically relevant divergence between MC and MI lies in the morphology and spatial logic of injury. MI is typically organized by coronary anatomy. Its pathology evolves along a relatively recognizable trajectory from ischemia to coagulative necrosis and finally to scar formation within a defined vascular territory [4, 14]. MC, in contrast, is structurally heterogeneous. It is often focal, sometimes epicardial or transmural, and may include intramyocardial hemorrhage, patchy tissue disruption, and sharply demarcated lesions that do not correspond to coronary distribution [45, 48]. Case-based and forensic observations likewise illustrate how blunt impact can produce irregular injury patterns that are anatomically and mechanically determined rather than territory-based [45, 46, 48].

This difference in injury geometry has important interpretive consequences. In MI, coronary territory remains central to the interpretation of symptoms, biomarker kinetics, electrocardiographic changes, and imaging findings. In MC, however, lesion distribution is often patchy, non-specific, or clinically obscured by associated thoracic trauma. As a result, literature increasingly favors multimodal assessment over reliance on any single diagnostic modality [47, 49]. Review data and imaging studies reinforce this preference for combined testing strategies in blunt cardiac injury [50, 51]. Multimodality imaging reports of cardiac contusion complications further support phenotype-based interpretation in ambiguous cases [52, 53]. Figure 1 summarizes this contrast by visually comparing the spatial and morphological logic of injury in MC and MI.

A broader trend in the field is therefore apparent. Work on MI has long emphasized territory-based pathological reasoning, whereas research on MC is gradually moving toward phenotype-based characterization, in which

FIG. 1. Comparative morphology and injury geometry of myocardial contusion and myocardial infarction



Note: MI — myocardial infarction; MC — myocardial contusion.

structural heterogeneity and clinical context are treated as defining features rather than diagnostic obstacles.

Biomarkers, electrocardiography, and imaging

Diagnostic evaluation represents another major area of divergence. In MI, high-sensitivity troponin is central but must be interpreted with symptoms, serial change, and electrocardiographic evidence rather than in isolation [54, 55]. Assay thresholds and assay transitions can further influence downstream clinical decisions [5, 56]. In MC, troponin is better understood as one component of risk stratification and exclusion. The dominant clinical approach supports combining admission electrocardiography with troponin testing, because concurrent normal findings substantially reduce the likelihood of clinically significant blunt cardiac injury [1, 57]. Experimental and clinical work also supports the biological relevance of troponin release after blunt cardiac trauma [58, 59]. Additional trauma studies underscore that risk depends on the broader injury pattern rather than biomarker elevation alone [60, 61]. This distinction is especially important when traumatic myocardial injury is evaluated against type 2 MI. A posttraumatic troponin rise should not be assigned reflexively to MC, type 1 MI, or type 2 MI. The universal definition requires evidence of acute ischemia before myocardial injury can be classified as infarction, whereas type 2 MI denotes ischemic injury caused by oxygen supply-demand imbalance without acute atherothrombosis [14, 20, 21]. In blunt chest trauma, hypoxemia, anemia, hypotension or hemorrhagic shock, and tachycardia or tachyarrhythmia may produce an oxygen supply–demand mismatch compatible with type 2 MI when accompanied by evidence of acute ischemia [14, 62, 63]; conversely, MC is favored by a compatible impact mechanism, focal traumatic wall-motion abnormality, pericardial or valvular injury, noncoronary injury geometry, and computed tomography (CT),

echocardiographic, or cardiac magnetic resonance evidence of structural trauma [52, 64, 65]. Selective CT and trauma-specific guidance further support imaging-based phenotyping when the mechanism and biomarker pattern are ambiguous [66, 67]. Therefore, diagnostic classification should integrate the mechanism of injury, hemodynamic trajectory, serial electrocardiogram (ECG) changes, troponin kinetics, imaging phenotype, and likelihood of acute coronary thrombosis before selecting an ACS pathway, anticoagulation, coronary angiography, or trauma-specific monitoring [9, 11, 68]. This distinction also aligns with practical recommendations for separating type 2 MI from acute nonischemic myocardial injury [62, 63, 69]. Table 1 summarizes the practical distinction between myocardial contusion and type 2 MI in trauma settings.

Electrocardiography follows a similar pattern of divergence. In MI, ST-segment elevation, dynamic ischemic change, and rhythm disturbance are interpreted within a structured and clinically actionable ischemic framework [9, 13]. Contemporary ACS guidance further reinforces this interpretive hierarchy [11]. In MC, electrocardiographic abnormalities may include sinus tachycardia, conduction delay, bundle branch block, ectopy, and nonspecific repolarization change, but these findings are neither sufficiently sensitive nor sufficiently specific to define diagnosis on their own [47, 70]. Delayed conduction disturbance after blunt cardiac injury also highlights the need for continued surveillance in selected patients [71, 72]. Trauma cohorts and experimental ECG studies show that arrhythmia burden reflects injury heterogeneity and procedural context with these observations summarized in a review that presents the full framework [73]. Experimental and review-based evidence supports the use of ECG primarily as a screening and monitoring tool in MC [1, 67, 74].

Imaging plays a broader phenotyping role in MC than in uncomplicated MI. Echocardiography remains valuable in both disorders, but in trauma it is especially useful for identifying wall-motion abnormalities, pericardial effusion, valvular injury, septal defects, and occult structural complications [47, 49, 50]. Cardiac magnetic resonance and selected computed tomography approaches further extend this role by helping distinguish blunt cardiac injury from acute coronary syndromes in diagnostically uncertain settings [18, 52]. Dual-energy CT feasibility data support this selective diagnostic expansion [66, 75]. Natriuretic peptide studies are also suggestive: NT-proBNP has been explored as a marker of blunt cardiac contusion [76], whereas after MI it retains prognostic value for subsequent ventricular risk [77, 78]. Overall, diagnostic literature suggests a clear trend: whereas MI relies on a comparatively standardized triad of symptoms, electrocardiography, and troponin dynamics, MC increasingly requires multimodal phenotyping adapted to the trauma context.

Table 1. Practical differentiation between myocardial contusion and type 2 MI in trauma settings

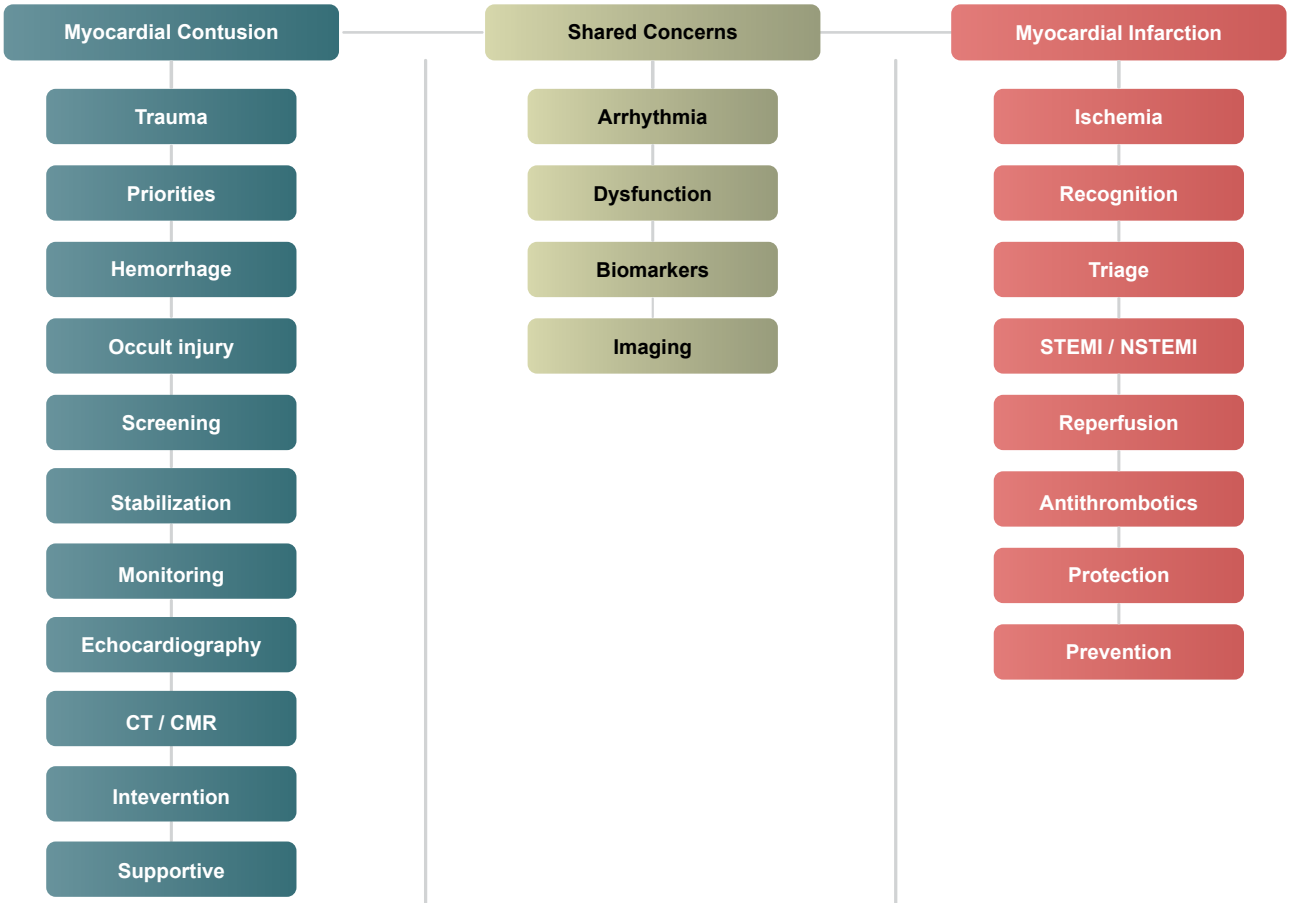
Dimension	Myocardial contusion	Type 2 myocardial infarction
Mechanism	Direct mechanical injury [3]	Supply-demand ischemia [14]
Trigger	Blunt chest trauma [3]	Anemia, hypoxemia, shock, tachyarrhythmia [14]
Electrocardiogram	Arrhythmia or conduction change [1]	Dynamic ischemic ST-T change [4]
Troponin kinetics	Variable trauma-related elevation [4]	Rise/fall with ischemic context [14]
Imaging	Focal noncoronary injury [5]	Ischemic or territory-based pattern [63]
Management	Stabilize, monitor, treat trauma [1]	Correct trigger; selective coronary work-up [63]

Therapeutic priorities and clinical pathways

The clearest divergence between MC and MI emerges in treatment strategy. MI is fundamentally an ischemia-centered and reperfusion-oriented disease, with care organized around rapid ischemic recognition, reperfusion or invasive evaluation when indicated, antithrombotic therapy, lipid-lowering therapy, and secondary prevention within contemporary ACS guideline frameworks [9, 11]. In parallel, cardiogenic shock, mechanical complications, post-infarction ventricular dysfunction, medication adherence, and long-term remodeling prevention are managed within an increasingly standardized continuum of care [79–81]. Mechanical complications after acute MI represent a distinct post-infarction management domain [82, 83].

MC follows a different clinical logic. The priority is not reperfusion but stabilization. Management is centered on hemodynamic support, rhythm monitoring, treatment of associated thoracic or extracardiac injuries, and selective evaluation of structural complications [1, 84]. Broader reviews of blunt thoracic and blunt cardiac trauma likewise frame MC within stabilization-first care pathways [15, 85]. In selected severe cases, suspected blunt cardiac injury may require urgent procedural or surgical evaluation for hemodynamic instability, tamponade, rupture, septal or valvular injury, traumatic arrest, or other mechanically significant cardiac lesions [67, 84, 86]. Trauma-focused resuscitation literature also supports emergency preservation or thoracotomy in selected catastrophic scenarios [87, 88]. Across age groups and procedural

FIG. 2. Divergent clinical pathways in traumatic and ischemic myocardial injury



Note: shared downstream injury does not imply identical management; myocardial contusion is stabilization-centered; myocardial infarction is reperfusion-centered; CT — computed tomography; CMR — cardiovascular magnetic resonance; STEMI — ST-elevation myocardial infarction; NSTEMI — non-ST-elevation myocardial infarction.

settings, arrhythmia surveillance and scenario-specific resuscitation remain central in suspected cardiac contusion [16, 73, 89]. Figure 2 summarizes this divergence in clinical logic by contrasting the stabilization-centered pathway of MC with the reperfusion-centered pathway of MI, while also highlighting the shared importance of rhythm surveillance and ventricular function assessment.

The major therapeutic conclusion of comparative literature is therefore twofold. First, direct transfer of MI algorithms to MC is generally inappropriate. Second, MC should not remain therapeutically under-theorized. The relevant opportunity is to test trauma-compatible adjunctive strategies aimed at inflammatory amplification, oxidative stress, receptor-signaling pathways, and maladaptive remodeling [34, 35]. Existing translational reviews of cardiac contusion provide further experimental rationale for such an approach [90, 91]. Experimental anti-inflammatory and biologically targeted interventions remain promising but investigational, and any future use in MC must be integrated without delaying life-saving trauma care [87, 92].

MI therefore provides mechanism-based hypotheses for MC, whereas MC does not offer a symmetrical treatment template for MI. Its reverse contribution is different: it reminds clinicians that myocardial injury management is inseparable from etiology, bleeding risk, structural injury, and treatment sequence.

Clinical significance of the comparison

The clinical value of comparing MC with MI lies in defining an asymmetric translational relationship. MI provides the more mature therapeutic framework, so its principal contribution to MC is conceptual: it supplies candidate mechanisms for adjunctive cardioprotection, remodeling control, and risk-oriented monitoring that may later be tested in trauma-specific settings [9, 11]. Reperfusion and ischemia-reperfusion literature provides the most relevant mechanistic basis for such hypothesis generation [7, 8]. Antifibrotic and remodeling-oriented work in MI further sharpens this hypothesis-generating role [42, 44]. MC, by contrast, does not offer a symmetrical treatment template for MI.

Conversely, MC's contribution to MI is qualitatively different. Because blunt cardiac injury is managed within a spectrum of bleeding risk, structural uncertainty, competing injuries, and staged stabilization, MC highlights the conditions under which canonical MI care remains appropriate and the point at which algorithmic transfer becomes misleading [4, 16]. Recent trauma-focused guidance makes this boundary problem even more explicit [67, 86]. This is why the key distinction is not between "similar" and "different" diseases, but between mechanistic portability and protocol portability.

A further contribution of the comparison is that it points toward a research agenda. The most urgent needs in MC include standardized phenotyping, better integration of biomarkers with imaging and monitoring, trauma-compatible diagnostic algorithms, and more systematic evaluation of ventricular and arrhythmic outcomes [17, 50]. Recent narrative and biomarker-focused reviews reinforce this agenda by emphasizing molecular characterization, biomarker validation, multimodal assessment, and the need for more systematic clinical data collection in blunt cardiac injury [17, 93]. More broadly, these priorities echo the developmental trajectory of MI research, in which descriptive pathological understanding was gradually linked to risk stratification and mechanism-based care. Based on this comparative synthesis, Table 2 summarizes the key domains that distinguish MC and MI in pathogenesis, diagnosis, and treatment, while also highlighting areas of partial overlap.

Table 2. Comparative characteristics of myocardial contusion and myocardial infarction across key domains of pathogenesis, diagnosis, and treatment

Domain	Myocardial contusion	Shared focus	Myocardial infarction
Injury mechanisms	Blunt trauma; patchy injury	Secondary injury biology	Ischemia-reperfusion; territorial loss
Biomarkers and imaging	Screening and phenotyping	Same modalities; different meaning	Risk stratification; coronary angiography
Clinical pathways	Stabilization in polytrauma	Rhythm and function assessment	Rapid ischemic triage
Therapeutic significance	Supportive and investigational care	Selective translational relevance	Reperfusion-centered management

The significance of this review is not that it proposes a unified model of myocardial injury. Its significance is that it refines the terms of comparison. It shows that true biological overlap should stimulate hypothesis-driven research, whereas superficial similarity should not justify therapeutic conflation. That distinction is precisely what makes the comparison clinically useful.

Limitations

Several limitations should be acknowledged. First, this is a narrative review rather than a formal systematic review or meta-analysis; accordingly, the present synthesis is interpretive and thematic rather than quantitatively pooled. Second, the evidence base for MC remains smaller and more heterogeneous than that for MI, with greater dependence on retrospective cohorts, mixed trauma populations, case series, and experimental models. Third, direct head-to-head comparative studies are scarce, which means that some of the conclusions necessarily derive from structured comparison across adjacent literatures rather than from unified datasets. Fourth, diagnostic definitions, biomarker thresholds, and imaging protocols for MC remain insufficiently standardized, limiting cross-study comparability.

Finally, this review primarily contrasts MC with the canonical ischemic architecture of MI, especially type 1 MI and reperfusion-centered ACS care. Although type 2 MI is addressed as a supply-demand mismatch syndrome, this article does not provide a complete diagnostic algorithm for separating MC from type 2 MI in trauma populations. This limitation is clinically relevant because polytrauma, hypoxemia, anemia, shock, tachyarrhythmia, systemic inflammation, and adrenergic stress may all produce dynamic troponin elevation and ischemic myocardial injury without primary coronary thrombosis; at the same time, MC may coexist with or mimic these processes through direct structural damage. Future comparative studies should therefore evaluate MC, type 2 MI, and acute nonischemic myocardial injury within a shared but etiologically stratified diagnostic framework (Table 3) [63, 66, 69].

Table 3. Research agenda for advancing comparative understanding of myocardial contusion and myocardial infarction

Stage 1 Current limitations	Stage 2 Immediate priorities	Stage 3 Mechanistic opportunities	Stage 4 Clinical translation
• Small evidence base • Heterogeneous definitions • Limited standardization • Scarce comparative data	• Trauma-specific phenotyping • Biomarker-imaging integration • Rhythm-risk stratification • Standardized follow-up	• Inflammation • Oxidative injury • Calcium dysregulation • Remodeling targets	• Selective intervention • Trauma-compatible algorithms • Risk-adapted surveillance • Precision supportive care

These limitations are not merely methodological constraints; they also reflect the current developmental stage of the field. In this sense, the uneven maturity of the two evidence bases is itself one of the central findings of the comparison.

Conclusions

MC and MI are linked by convergent secondary injury biology, yet they remain clinically non-equivalent conditions defined by distinct initiating insults, spatial patterns of damage, diagnostic frameworks, and therapeutic priorities. Their comparison is therefore informative only when mechanistic overlap is interpreted alongside irreducible differences in clinical context.

The central conclusion of this review is that the relationship between MC and MI is translationally asymmetric. MI provides a more mature mechanistic framework from which biologically plausible hypotheses may be derived for MC, particularly in relation to inflammatory amplification, oxidative injury, maladaptive remodeling, rhythm-risk surveillance, and integrated biomarker–imaging assessment. However, this translational relevance is selective rather than algorithmic. Reperfusion-centered management, routine ACS antithrombotic strategies, and coronary-occlusion-based decision pathways remain specific to ischemic disease and should not be extrapolated uncritically to traumatic myocardial injury.

Conversely, the value of MC lies not in serving as a therapeutic analogue of MI, but in exposing the contextual limits of canonical MI care. By embedding myocardial injury within a trauma setting shaped by bleeding risk, structural uncertainty, competing injuries, and staged stabilization, MC makes clear that myocardial injury management cannot be separated from etiology and clinical sequence. Future research should prioritize trauma-specific phenotyping, multimodal stratification, and prospective evaluation of adjunctive targeted therapies that can be integrated into trauma-first care without delaying stabilization.

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Fundamental Pharmacology

Original article

Function of the sodium-calcium exchanger during myocardial contraction-relaxation caused by strophanthin administration

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ABSTRACT

Cardiac glycosides influence myocardial contractility via affecting Na^+–Ca^{2+} exchange, but the isolated contribution of this mechanism remains poorly understood.

Aim. To determine the effects of strophanthin on cardiac contractions generated by the sodium-calcium exchange system alone.

Materials and methods. Experiments were performed on isolated hearts of Wistar laboratory rats perfused through the aorta using the Langendorff technique. Contractions were induced by perfusion with solutions of varying Na^+ concentrations. Strophanthin in ampoules that was used as the studied pharmaceuticals was added to the perfusion medium at a final concentration up to 0.5 μmol/L. An equivalent volume of saline was administered in the control series.

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.
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Data sharing: The data confirming the findings of this study are available from the authors upon reasonable request. Data and statistical methods used in the article were examined by a professional biostatistician on The Eurasian Journal of Life Sciences editorial staff.

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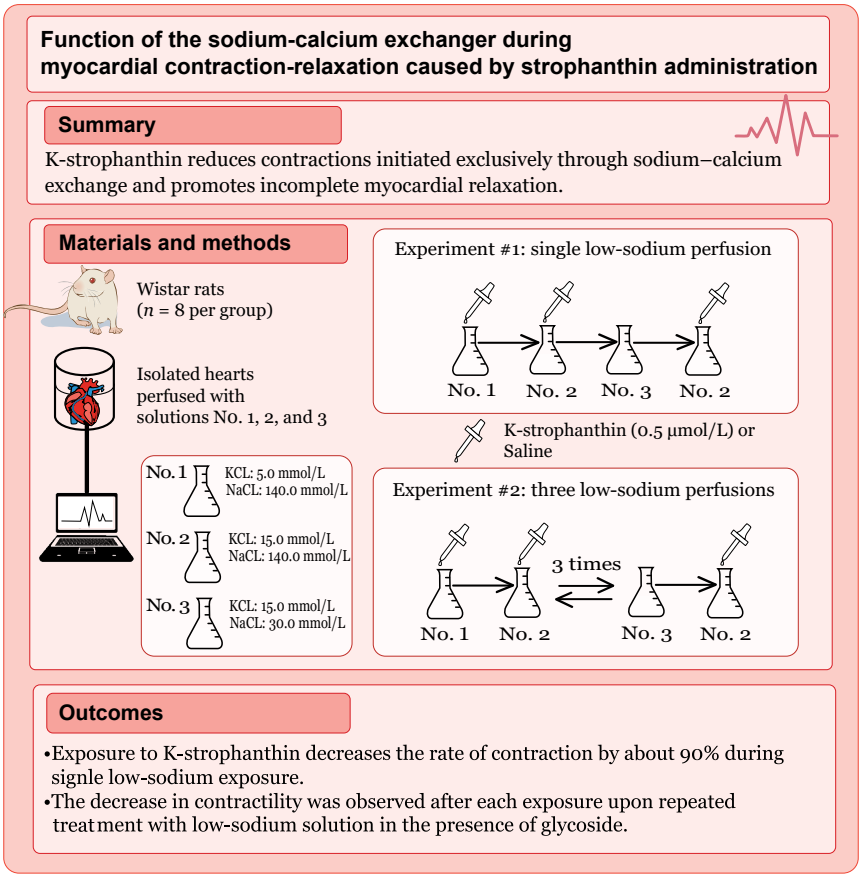
Results. Experiments showed that the heart continued to contract and relax with each cycle of Na^+–Ca^{2+}exchange activation. However, the rate of contraction in the second repetition was 32% lower. Strophanthin reduced contraction force in all three repetitions. Particularly significant disturbances were observed during the first stimulation — by 78%. Muscle contractions and relaxation occurred under gradual increase in muscle tone during diastole. Given that strophanthin can reduce the activity of the Na^+/K^+-Adenosine Triphosphatase (Na^+/K^+-ATPase), our experiments clearly demonstrated the glycoside's ability to increase intracellular sodium, and consequently, calcium concentrations. Repeated calcium efflux from cells via Na^+–Ca^{2+}exchange proved ineffective in the presence of strophanthin. The heart continued to experience calcium overload, which was reflected in the increased cardiac diastole stress.

Conclusion. When cardiac cells experience calcium ion overload, the final physiological effect influenced by strophanthin may be negative rather than positive.

Graphical abstract



Key Words: Na^+–Ca^{2+} metabolism; strophanthin; cardiac calcium overload; sarcoplasmic reticulum; voltage-dependent channels; cardiac glycosides

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MeSH terms:

MYOCARDIAL CONTRACTION — DRUG EFFECTS;

MYOCARDIUM — METABOLISM;

STROPHANTHIDIN — PHARMACOLOGY;

SODIUM-CALCIUM EXCHANGER — DRUG EFFECTS

Introduction

In clinical practice, pharmaceuticals that enhance the functional capacity of the cardiac muscle are widely used. Cardiac glycosides, such as strophanthin, which has a pronounced positive inotropic effect, are of special significance among them. The pharmacological effect of glycosides is associated with their ability to inhibit Na^+/K^+-Adenosine Triphosphatase (Na^+/K^+-ATPase) in the cell membrane. Blockade of this enzyme leads to an increased intracellular sodium content, which activates Na^+–Ca^{2+} exchange carried out by a specialized transporter in the outer membrane of cardiomyocytes [2, 3]. The Na^+–Ca^{2+}transporter protein is capable of binding and transporting ions of both types; however, at rest, the Na^+ and Ca^{2+} interaction with its active site is balanced, and practically no transport is performed. When the sodium concentration in the cytoplasm increases under the influence of glycosides, Na^+ obtains an advantage, and the exchanger starts to effectively remove sodium from the cell replacing in exchange for calcium. This results in an increase in the intracellular mobile fraction of Ca^{2+} circulating between the cytosol and the sarcoplasmic reticulum, and consequently an enhanced myofibrils activation and increased contraction force. Under normal conditions, cardiomyocyte contraction is triggered by a small amount of calcium entering through L-type calcium channels during electrical stimulation. This initial influx serves as a stimulus for ryanodine receptors, causing a massive release of Ca^{2+} from the reticulum [4].

This mechanism has been well studied, but the involvement of Na^+–Ca^{2+} exchange as a secondary mechanism for activating calcium release remains controversial. As supposed, an increased local sodium concentration in the subsarcolemmal space under fast sodium channels opening during an action potential can enhance Ca^{2+} entry via Na^+–Ca^{2+}exchange [5, 6]. During depolarization by fast Na^+ currents, sodium concentration at the inner surface of the membrane increases, and excess sodium is exchanged for extracellular calcium. As a result, intracellular Ca^{2+} increases which may further contribute to the activation of ryanodine receptors [7].

Since the activity of Na^+–Ca^{2+} exchange is determined by the level of intracellular Na^+, and cardiac glycosides significantly increase its content, the action of the second triggering mechanism can be significantly altered [3]. A decrease in the sodium gradient weakens the Na^+ in flux during the action potential and can reduce the efficiency of Ca^{2+} entry mediated by Na^+–Ca^{2+} exchange. Therefore, the extent to which cardiac glycosides are able to modify the force of cardiac contractions arising exclusively through Na^+–Ca^{2+} exchange remains unknown. To clarify this, it is necessary to exclude all other pathways for Ca^{2+} and Na^+ ion influx through channels and to initiate contraction through Na^+–Ca^{2+} exchange alone.

An important prerequisite for studying the sodium-dependent movement of calcium ions across the muscle sarcolemma is the elimination of other calcium fluxes. Calcium ions can enter cells through slow calcium channels and be excreted by Ca^{2+} pumps. Fast sodium channels may also be involved in the regulation of intracellular Ca^{2+} levels. The appearance of sodium ions inside cells can also alter the Na^+–Ca^{2+} exchange process, this additionally being an interfering factor when assessing the function of the sodium-calcium exchanger alone [7]. Therefore, the best way to eliminate these interferences, in the study of exclusively Na^+–Ca^{2+} exchange, is the complete shut-off of sodium and calcium channels by depolarisation of cardiomyocyte membranes.

The aim of this study was to determine the nature of strophanthin effect on the calciumdependent mechanical activity of the heart triggered exclusively through the sodium-calcium exchange mechanism.

Materials and methods

Laboratory animals

Thirty-two mature male Wistar rats weighing between 180 and 250 g, and aged 2–3 months were used in a series of experiments. Animals were obtained from the Research Institute of Experimental Biology and Medicine of the N.N. Burdenko Voronezh State Medical University. The experiments were conducted in accordance with the recommendations of the Eurasian Economic Commission No. 33. The studies were approved by the local independent ethics committee, N.N. Burdenko Voronezh State Medical University (Protocol No. 5 dated 19.09.2023).

Isolation of heart

Animals were euthanized by decapitation using a desiccator under general anesthesia with diethyl ether. Immediately after thoracotomy, the isolated heart was placed in cooled (2–4 °C) Krebs—Henseleit solution. After spontaneous contractions ceased, the heart was cannulated through the aorta, and cardiac perfusion was performed. Perfusion was performed at a stable rate of 9 ml/min per 1 g of wet heart weight. There were two experiments performed. Each experiment involved 16 animals: 8 rats in control group and 8 animals in experimental group.

Equipment and perfusion solutions

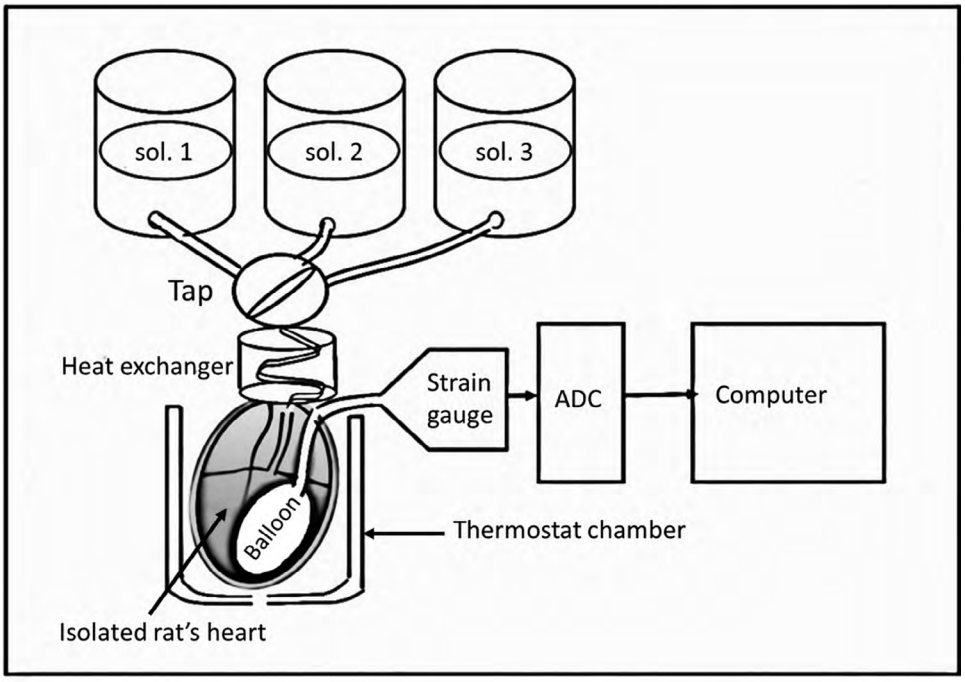
Elastic balloons were fixed in the left ventricular cavity and connected to an electronic pressure sensor. The described construction was used to record contractile parameters. Sensor signals were amplified, sent to an analog-to-digital converter, and then analyzed using the Zet Lab software module connected to a personal computer (Figure 1). Zet Lab software was used to record and process the studied parameters. Such a model has already been successfully employed by us in the course of other studies [8].

Oxygenated Ringer-Locke solution (solution No. 1) was used as the base perfusion solution at 37 °C. Solutions No. 2 and No. 3 characterized by an increased potassium chloride concentration of 15 mmol/L and used to create depolarization conditions. The increased K^+ level led to persistent depolarization of the cardiomyocyte membrane; thus, sodium and calcium voltage-gated channels lost their ability to open in response electrical activity.

The composition of the perfusion solutions used is presented in Table 1.

After the isolated heart was connected to the perfusion apparatus, stabilization of cardiac function was achieved by perfusing with solution No. 1 for 10 minutes. The heart was switched to solution No. 2 containing a three-fold concentration of KCl before the activation of sodium-calcium exchange. This technique resulted in a complete cessation of electrical and mechanical activity, eliminating the entry of Ca^{2+} through L-channels and the Na^+ current associated with action potential [9]. Thus, the only mechanism remained capable of initiating the release of Ca^{2+} from the sarcoplasmic reticulum and causing contraction was Na^+–Ca^{2+} exchange. Sodium-dependent calcium influx was initiated by replacing the standard solution with hyponatremic solution No. 3, in which the NaCl concentration was reduced from 140 to 30 mmol/L. With reduced sodium concentration in the extracellular medium,

FIG. 1. Schematic diagram of a device recording cardiac contractions via Na^+–Ca^{2+} exchange [8]



Note: ADC — analog-to-digital converter; sol. — solution.

Table 1. Composition of perfusion solutions

Components	Solution No. 1	Solution No. 2	Solution No. 3
NaCl	140.0	140.0	30.0
$NaHCO_3$	2.0	2.0	2.0
KCl	5.0	15.0	15.0
Tris-OH (pH = 7.4)	2.0	2.0	2.0
$CaCl_2$	2.0	2.0	2.0
Glucose	11.0	11.0	11.0
Mannitol	–	–	220.0

Note: all concentrations are given in mmol/L.

calcium ions obtained an advantage while interacting with the Na^+–Ca^{2+}-exchanger on the outer membrane surface, leading to increased Ca^{2+} entry into cells. The decrease in osmolarity of the hyponatremic solution No. 3 was compensated by adding mannitol (up to the final concentration of 220 mmol/L). After 5-min perfusion with the hyponatremic solution No. 3, it was replaced with the solution No. 2, containing NaCl and KCl at their original concentrations of 140 mmol/L and 15 mmol/L, respectively. Under these conditions, the direction of Na^+–Ca^{2+} exchange was reversed: excess extracellular Na^+ entered the cells, while Ca^{2+} was removed from the cytosol.

The sequence of solutions' application in first experiment was as follows: solution No. 1 (10 min) → solution No. 2 (5 min) → solution No. 3 (5 min) → solution No. 2 (5 min).

Following the first experiment (16 rats), a second experiment was performed. It involved three consecutive activations of the Na^+–Ca^{2+} exchanger to elucidate the mechanisms underlying the effect of K-Strophanthin (hereafter referred to as strophanthin) on calcium regulation of myocardial contractility. The sequence of solutions' application in the second experiment was as follows: solution No. 1 (10 min) → [solution No. 2 (5 min) → solution No. 3 (5 min)] × 3 times → solution No. 2 (5 min).

Strophanthin in ampoules was added to the perfusion medium of the solutions No. 1 and No. 2 that were used in experimental groups to a final concentration up to 0.5 μmol/L. An equivalent volume of saline was administered to the solution used in animals of the control group.

The complete experimental design is presented in Figure 2.

FIG. 2. The experimental design for studying the effect of strophanthin on the function of the Na^+–Ca^{2+} exchanger

First experiment:

Control: Saline (8 rats)

Experimental: 0.5 μmol/L strophanthin (8 rats)

Sol. 1	Sol. 2	Sol. 3	Sol. 2
10 min	5 min	5 min	5 min

Second experiment:

Control: Saline (8 rats)

Experimental: 0.5 μmol/L strophanthin (8 rats)

Sol. 1	Sol. 2	Sol. 3	Sol. 2	Sol. 3	Sol. 2	Sol. 3	Sol. 2
10 min	5 min	5 min	5 min	5 min	5 min	5 min	5 min

Note: Sol. – solution.

Statistical analysis

Statistical data were processed using repeated-measures analysis of variance (RM-ANOVA). The normality of distribution was assessed using the Shapiro–Wilk test. The significance of differences between the mean values of the experimental and control groups was assessed using paired *t*-test (when comparing between time points) and independent Student's *t*-test (when comparing between groups). Differences were considered statistically significant in $p < 0.05$. Statistical data were analyzed using StatSoft (TIBCO Statistica 14.1.0).

Results

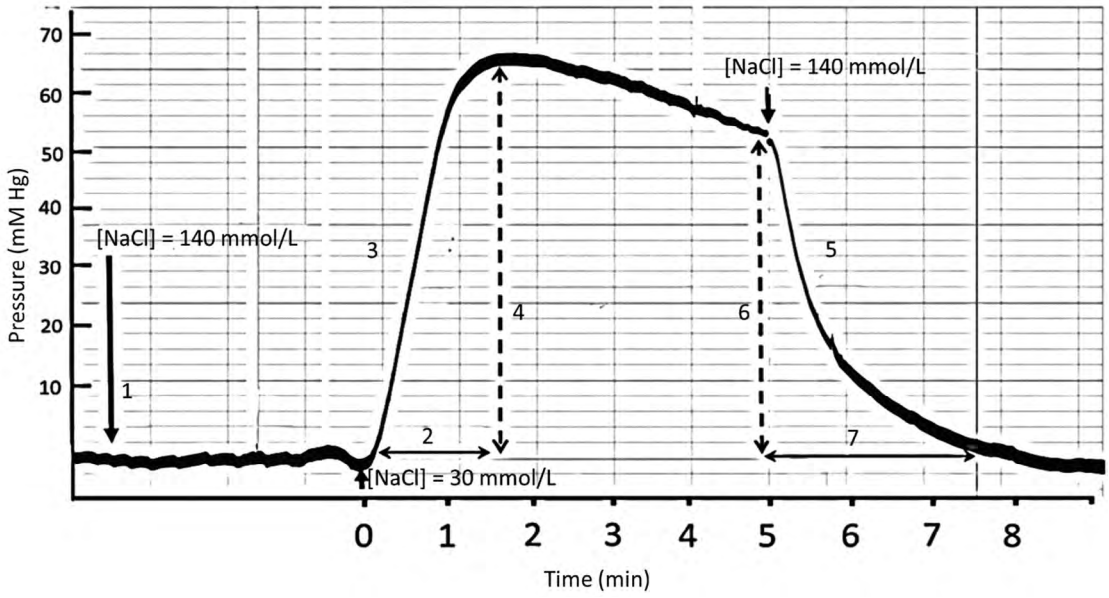
All experiments were conducted under complete asystole. This approach fully eliminated the involvement of calcium currents through L-type channels, as well as the inward sodium currents that accompanied action potential. This allowed the occurrence of mechanical activity to be associated exclusively with the functioning of the Na^+–Ca^{2+} exchange mechanism.

Cardiac response to strophanthin during a single low-sodium perfusion

The Na^+–Ca^{2+} exchanger activation by decreased extracellular sodium levels under the control conditions resulted in left ventricular contraction (Figure 3). The contraction demonstrated its maximum pressure, reaching 63 mmHg, approximately 74 seconds after the onset of hyponatremic solution perfusion.

Reversion to a solution with a normal NaCl concentration within five minutes caused gradual muscle relaxation and restoration of the initial tone. These observations confirmed that altering the direction and intensity of the Na^+–Ca^{2+} exchanger allowed both initiating and terminating the left ventricular mechanical activity. Thus, Na^+–Ca^{2+} exchange under these conditions influenced not only the force of contraction but also the relaxation phase of the myocardium.

FIG. 3. Recording changes in pressure in the left ventricle of the heart under the activation of Na^+–Ca^{2+} exchange via changing the extracellular concentration of sodium chloride

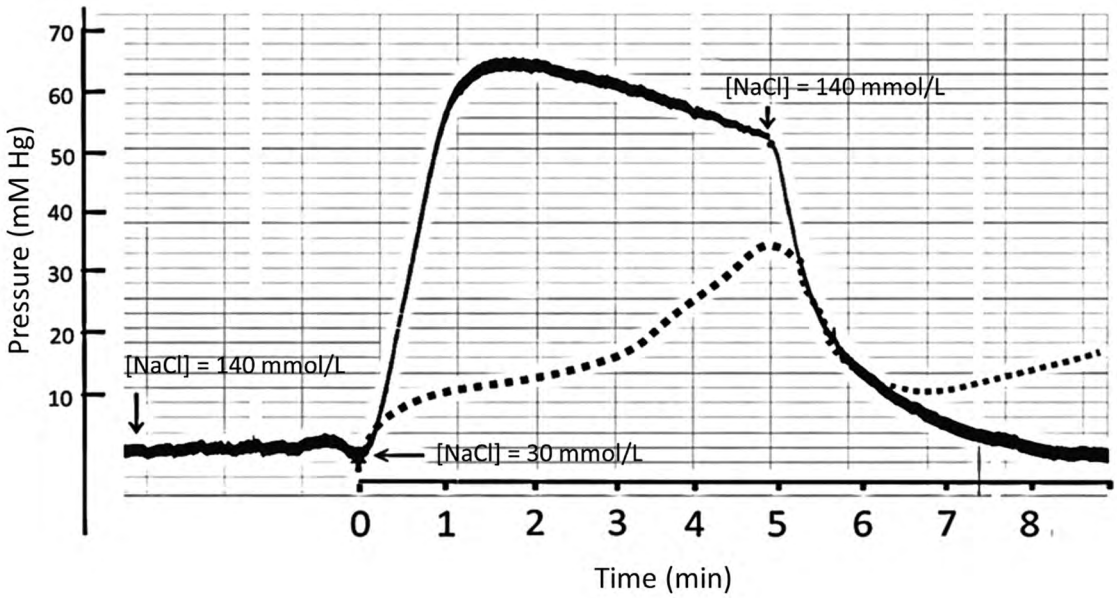


Note: 1 – initial pressure, 2 – T1 contraction, 3 – V Contraction, 4 – H1 max contraction, 5 – V Relaxation, 6 – H2 min relaxation, 7 – T2 relaxation.

The tension parameters, the rate of contraction increase, and the rate of relaxation were subjected to mathematical analysis, which allowed developing a model for further evaluation of the strophanthin effect under conditions where contractility was regulated exclusively by the Na^+–Ca^{2+} exchange system.

After pre-perfusion with a solution containing strophanthin, Na^+–Ca^{2+} exchange was activated by reducing the extracellular Na^+ concentration to 30 mmol/L. The cardiac response in this case was significantly different from the control (Figure 4).

FIG. 4. The strophanthin effect on the dynamics of contraction and relaxation of the rat heart caused by the Na^+–Ca^{2+} exchange activation



Note: the dashed line indicates the values of the experimental group (n = 8) that received strophanthin, and the solid line indicates the values of the control group (n = 8) that was administered saline.

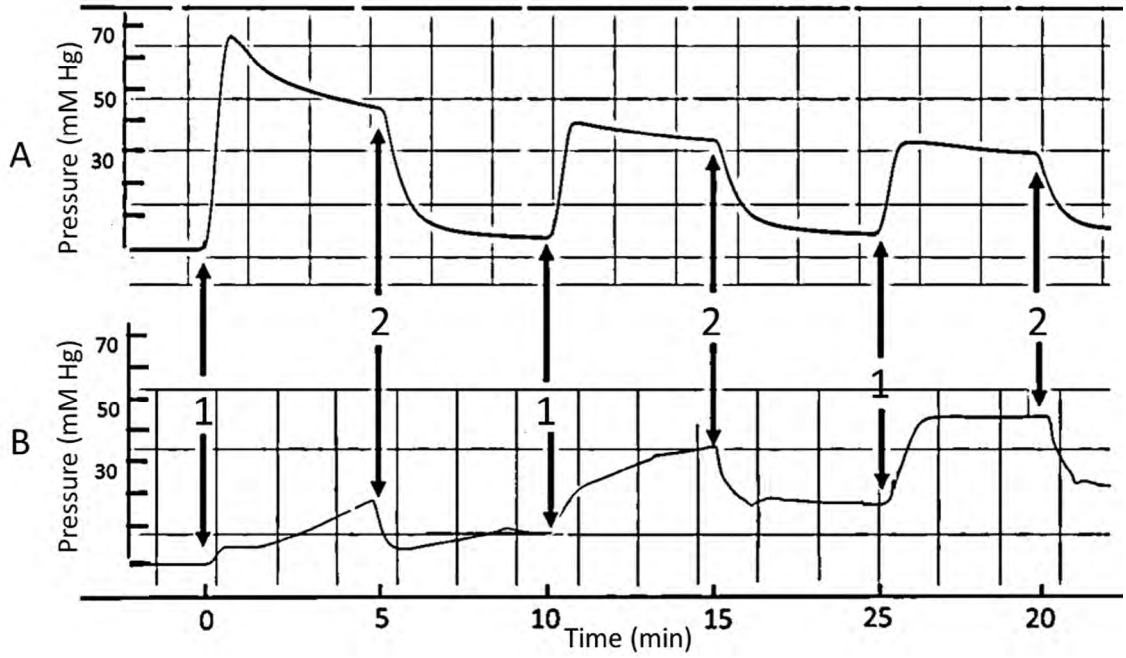
There was a sharp decrease in the rate of contraction development—approximately 90%. Maximum contractile force decreased by 80%. Even after 5-min-perfusion via a hyponatremic solution, tension levels remained 50% lower than the control values. These data indicated a significant strophanthin effect on myocardial contractility via calcium regulation.

Cardiac response to strophanthin during three successive low-sodium perfusions

The next step was to determine how strophanthin influences cardiac contractility under repeated stimulation of Na^+–Ca^{2+} exchange. Accordingly, we performed additional experiments, including three successive exchanger activations via extracellular Na^+ reduction.

The heart retained its ability to contract and relax with each cycle of Na^+–Ca^{2+} stimulation. However, in the second cycle, the rate of contraction development decreased by 32% compared to the first cycle (Figure 5).

FIG. 5. Strophanthin effect on repeated contractions and relaxations of the heart stimulated by Na^+–Ca^{2+} exchange



Note: the recordings of changes in left ventricular pressure during repeated activations of Na^+–Ca^{2+} exchange in the control group (A) and the experimental group (B). The activation was performed with varying concentrations of NaCl — 30 mmol/L (1) and 140 mmol/L (2). The number of animals was 8 in each group.

Strophanthin reduced contractile force in all three repeated activations, most significantly in the first (by 78%), then in the second (by 24%), and to the least extent in the third (by 20%). A gradual increase in diastolic tone was observed (Table 2), indicating incomplete muscle relaxation after each cycle.

The fact that the heart maintained its ability to respond to repeated changes in the direction of Na^+–Ca^{2+} exchange indicates that the exchanger continued to function even in the presence of strophanthin. Furthermore, the preservation of contractile responses during repeated activations confirmed the sarcoplasmic reticulum functionality. Thus, repeated cycles of Na^+–Ca^{2+} exchange activation in the presence of strophanthin were accompanied by an ever-growing decrease in the amplitude of incoming calcium flows and resulted in weakened contractions.

Table 2. Strophanthin effect on the values of Na^+–Ca^{2+} exchange reactions during three successive contractions and relaxations

Parameters	The number of repeated Na^+–Ca^{2+}exchanges			
	Experiments	1st cycle	2nd cycle	3rd cycle
V1, the rate of increased systolic tone ($dP/dt_{max}/c$)	control	1.31 ± 0.02	1.25 ±0.03	1.20 ± 0.04
	strophanthin	0.13 ±0.01**	0.85 ± 0.06** #	1.10 ± 0.05#
V2, the relaxation rate ($dP/dt_{max}/c$)	control	0.98 ± 0.03	0.94 ± 0.02	0.91 ± 0.03
	strophanthin	0.87 ± 0.04*	1.05 ± 0.04* #	0.84 ± 0.05
Maximum contractile force, H1 (mmHg)	control	63 ± 1.3	58 ± 1.4#	55 ± 1.1#
	strophanthin	14 ± 1.0**	44 ± 1.9** #	44 ± 1.7* #
Contractile force in 5 minutes of 30-mM-NaCl perfusion, H2 (mmHg)	control	49 ±1.4	48 ±1.06	48 ± 1.0
	strophanthin	26 ± 1.3**	38 ± 1.9** #	36 ± 1.4*#
The time period from the onset of the Na–Ca exchange initiation to the maximum reduction, T1 (sec)	control	74 ± 2.1	77 ± 1.2	72 ± 1.5
	strophanthin	290 ± 14**	81 ± 2.1#	78 ± 0.9#
The time period from the onset to complete muscle relaxation, T2 (sec)	control	130 ± 2.7	125 ±3.2	117 ± 2.4
	strophanthin	125 ± 6.4	118 ± 5.7	116 ± 2.9

Note: data is presented as the mean ± standard error of the mean (SEM); * — $p < 0.05$ and ** — $p < 0.01$ by independent Student's *t*-test when compared with control; # — $p < 0.05$ by paired *t*-test when compared with 1 record within the same group. Both control and experimental groups included 8 rats.

Calcium removal upon returning to normal sodium solution was also incomplete: although the rate and duration of the relaxation phase did not differ from the control, the initial tone level remained elevated in each case. Thus, strophanthin maintained a chronically elevated Ca^{2+} concentration in cytosol throughout the experiment, leading to a persistent increase in diastolic tension and incomplete recovery of the muscle potentials between activation cycles.

Discussion

First, we should emphasize the validity of the chosen experimental technique. Conditions of complete electrical activity blockade and cardiac contractions cessation allowed recording mechanical responses arising exclusively via the sodium-calcium exchange mechanism.

A distinctive feature of the identified process was that contractions developed significantly more slowly than under physiological conditions of electromechanical activation. This indicated that calcium entering cells via Na^+–Ca^{2+} exchange not only triggered the release of ions from the sarcoplasmic reticulum but also directly activated the contractile apparatus. This assumption is consistent with Lehnart et al. who demonstrated the ability of calcium entering via Na^+–Ca^{2+} exchange to interact with the contractile structures of cardiomyocytes [10].

Furthermore, Na^+–Ca^{2+} exchange, under certain conditions, has the potential to provide a sufficient Ca^{2+} influx to maintain contractile activity even during a normal action potential. For example, it has been shown that blockade of the Na^+–Ca^{2+} exchanger led to a shortening of the action potential and a marked reduction in contractile force [11].

It is important to note that the maximum pressure developed in the rat left ventricle with sodium-dependent Ca^{2+} influx was comparable to the level observed in physiological and pathological conditions of the heart [12]. These data confirm the validity of the chosen approach to analyze the effect of glycosides on the calcium exchange mechanism regulating contractility.

Strophanthin reliably increases intracellular calcium levels via Na^+/K^+-ATPase inhibition and activation of the Na^+–Ca^{2+} exchange. This compound was chosen as a model medication to evaluate the effect of glycosides on

the activity of Na^+-Ca^{2+} exchanger. In clinical practice, however, strophanthin requires caution: in severe heart failure, arrhythmia, or ischemic injury, the use of glycosides is limited due to the potential for deterioration in energy metabolism and electrolyte balance [13, 14].

The positive inotropic effect of strophanthin is associated with an increase in the free fraction of intracellular calcium. However, in various pathological conditions, decreased activity of the Na^+–K^+ pump itself can lead to accumulation of intracellular Na^+ and a secondary increase in Ca^{2+} via Na^+–Ca^{2+}exchange. These processes accompany the development of local contractures and other disorders associated with myocardial contractility [10, 15].

Glycoside administration under pre-existing calcium overload can reduce rather than enhance cardiac performance and increase the risk of arrhythmia, as has been repeatedly reported in clinical observations [14, 16].

The study results confirm these concerns. As demonstrated, the developing myocardial calcium overload is the main factor in the pronounced weakening of contractions upon strophanthin treatment. These data are consistent with the idea that excess cytosolic Ca^{2+} can suppress the activity of the Na^+–Ca^{2+} exchanger at the stage of its direct action [17]. This is evidenced by the following experimentally observed phenomena:

- slowdown in the rate of contraction development;
- decrease in the maximum force of contraction;
- incomplete muscle relaxation under reversion to a normal sodium environment;
- gradual increase in diastolic tension.

These effects are particularly significant under conditions when strophanthin maintains elevated intracellular Na^+ levels for a long time. Sodium accumulation naturally leads to an increased Ca^{2+} concentration; the exchanger is unable to completely remove this excess under reversion to a normal sodium solution. This results in a persistently increased cardiac tone and incomplete relaxation after each cycle of Na^+–Ca^{2+} exchange activation.

The presented study has a number of limitations that should be acknowledged. The results came from experiments on isolated rat hearts that were prepared under conditions of artificial perfusion, thus, may not directly reflect all aspects of heart function *in vivo*. Also, the observed alterations of the perfusion rate may be impacted by the changes in heart muscle activity or individual parameters of each rat. The conclusions regarding changes in Na^+–Ca^{2+} exchange are based on indirect measurements. In particular, we did not measure Na^+/K^+-ATPase activity or the expression of transporter proteins. However, the correlation between heart contractility and the ionic composition of the environment is well known [18]. Therefore, in our opinion, these conclusions are reasonable and the importance of the results remains.

Conclusion

In this study, strophanthin reduced contractions initiated exclusively through Na^+–Ca^{2+} exchange and promoted incomplete myocardial relaxation. The data obtained demonstrate that the use of cardiac glycosides is only justified when the cellular ability to regulate intracellular Ca^{2+} levels is preserved. Under calcium overload, the cardiac glycoside effect may be unfavorable and, instead of enhancing, may actually suppress myocardial contractility.

These results additionally evidence that the efficacy and safety of glycosides are closely related to the initial state of ionic homeostasis of the cardiac muscle and should be taken into consideration during clinical use.

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Microbiomics and Metagenomics

Original article

Is there an association between vaginal, urethral and urinary microbiota in women with urogenital tract diseases?

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ABSTRACT

Urinary tract infections (UTI), including recurrent cystitis, are usually interpreted in relation to dominant uropathogens. However, the microbial context of adjacent urogenital sites may also be relevant.

Aim. To evaluate the association between UTI and the microbiota of different parts of the urogenital tract in order to provide insights into disease pathogenesis and treatment.

Material and methods. The study included three groups: healthy volunteer group ($n = 34$); patients at risk of developing UTI (women with micronephrolithiasis

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and/or bacterial vaginosis; *n* = 16); and patients with a history of recurrent lower UTI (*n* = 100). Four types of biomaterial were used: first-pass and midstream urine samples, urethral and vaginal swabs. All samples were analyzed by multiplex real-time polymerase chain reaction reagent kits Femoflor®16 and BacScreen OM.

Results. Genomic DNA and total bacterial quantities increased while relative lactobacilli decreased in patients with a risk of UTI and in those with recurrent lower UTI. This was only the case in midstream and first-pass urine samples. Relative lactobacilli levels in the urethral and vaginal swabs were only slightly but statistically significantly reduced in patients with recurrent lower UTI. Facultative anaerobes predominated in urine samples of patients with a risk of UTI, while in patients with recurrent lower UTI an increase in both facultative and obligate anaerobes was observed.

Conclusion. Midstream and first-pass urine samples can reliably assess inflammation in the urogenital tract. No strict correlation was observed between the vaginal and urinary microbiota of patients with recurrent lower UTI, meaning that UTI do not necessarily affect the vaginal biotope.

Key Words: RT-PCR; dysbiosis; lactobacilli deficiency; recurrent lower UTI; type specimen

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URINARY TRACT INFECTIONS — MICROBIOLOGY
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MICROBIOTA

Introduction

It is beyond doubt that *Enterobacterales* representatives, mainly *E. coli*, are the leading cause of urinary tract infections (UTI). Vazquez-Montes et al. show that *E. coli* was detected in 65% of positive urine cultures overall and in 68% of index episodes among women with recurrent UTI in a large community-based cohort of women [1]. However, it is also undeniable that UTI and recurrent UTI have a broader etiological spectrum [2].

UTIs are significantly more prevalent in women compared to men [3]. Clearly, the urinary tract microbiota of women differs from that of men: normally, the former is dominated by lactobacilli (LB), as is the adjacent genital biotope [4]. Evidence from numerous clinical studies summarized in reviews shows that a woman's vaginal microbiota affects her susceptibility to UTI [2, 5]. For example, women with bacterial vaginosis (BV) have a higher risk of developing UTI compared to women with a predominance of LB in the vaginal microbiota [2, 6–8]. In addition, clinical trials and reviews have shown that treatments affecting the microbiota (e.g., vaginal probiotics and estrogens) may protect against new relapse episodes of recurrent UTI [2, 9, 10]. Thus, these findings support an association between the female genitourinary microbiota and the development of UTI. However, the precise mechanisms underlying this relationship remain the subject of ongoing clinical research.

With the introduction of molecular techniques, there emerged more possibilities for detecting difficult or unculturable bacteria compared to classical culture methods. Non-culture-based methods also make it possible to assess

quantitative ratios of bacteria in a sample, irrespective of their viability and culturing requirements [11]. Thus, these findings support an association between the female genitourinary microbiota and the development of UTI. However, the precise mechanisms underlying this relationship remain the subject of ongoing clinical research. Moreover, the use of such methods enables a broader microbiological assessment involving different types of biological specimens. Previously, we investigated the contribution of urinary microbiota assessed in midstream urine samples in patients with chronic cystitis [12]. Building on these findings and on evidence that the urinary and vaginal microbiomes are closely linked, we performed an extended evaluation of microbiota from additional sources to assess their diagnostic value [13, 14]. This approach may provide a more comprehensive understanding of the microbial composition of the female genitourinary tract in the context of the infectious process.

The aim of this study was to evaluate the association between urinary tract infections and the microbiota of different biotopes of the urogenital tract in order to provide insights into disease pathogenesis and treatment.

Materials and methods

Study design

This multicenter, observational, cross-sectional comparative study was conducted to evaluate and compare microbiota profiles in four types of urogenital specimens obtained from women with recurrent lower UTI, women at increased risk of UTI, and healthy controls. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Sechenov University Institutional Reviewer Board, protocol No. 152, dated 20 April 2022.

Setting

The study was conducted at “On Clicic Lux LLC” (Moscow), State Budgetary Institution “GP 46 DZM” (Moscow), and Semeynaya Poliklinika #4 LLC (Korolev), Russia, between April 2022 and May 2023. Participant recruitment and specimen collection were performed during routine outpatient evaluation. Given the nature of the cross-sectional design, no longitudinal follow-up was planned.

Participants

An informed consent, signed and dated by a patient, was obtained prior to conducting any study-related procedures. Non-pregnant women of reproductive age from 18 to 45 years old were enrolled in the study. The exclusion criterion for all participants was acute (and relapses of chronic) vulvovaginitis due to sexually transmitted infections. Three study groups have been formed.

The first group (“Control”) included healthy volunteers, with no dysuria and/or other complaints indicative of UTI, absence of symptoms and signs of chronic inflammatory urogenital tract diseases; absence of changes in general urinalysis and non-use of antibacterial medications within the last 3 months. Participants in this group were excluded from the study if they had received glucocorticosteroids or any other immunosuppressant (due to autoimmune diseases) or intravaginal medications, including contraceptives, within the last 3 months.

The second group (“Risk of UTI”) included patients with no dysuria and/or other complaints indicative of UTI, but with micronephrolithiasis or/and BV

verified during assessment and non-use of antibacterial medications within the last 3 months. Participants in this group were excluded if they had received glucocorticosteroids or any other immunosuppressant (due to autoimmune diseases) or intravaginal medications, including contraceptives, within the last 3 months.

The third group included patients with a history of recurrent lower UTI "rLUTI" defined as two relapse episodes within six months or three episodes within one year; clinically and laboratory confirmed relapse of rLUTI; incapable of childbearing, or capable of childbearing but with negative pregnancy test at the primary visit and agreement to consistently and appropriately use one of the acceptable contraception methods. Exclusion criteria were as follows: postcoital cystitis; complicated UTI; pregnancy planning in the next 6 months; absence of laboratory verification of rLUTI; identification of sexually transmitted infections; non-adherence to the prescribed medication regimen or presence of side effects; patient withdrawal from further participation in the study.

After screening (n = 172), a total of 150 participants were enrolled in the study: 34 participants in the "Control" group, 16 patients in the "Risk of UTI" group, and 100 patients in the "rLUTI" group.

Variables

The primary study variables were the human genomic DNA signal, total bacterial load, the relative abundance of *Lactobacillus* spp., and the relative abundance of facultative and obligate anaerobic microorganisms in each specimen type.

Data sources / measurement

The clinical specimen for the study were the first-pass and midstream samples of morning freely discharged urine obtained after genital toilet, urethral swabs obtained prior to urination and swabs from the posterolateral vaginal wall. All specimens were collected on the same day.

DNA extraction was performed from freshly obtained urine samples and urethral and vaginal swabs using a PREP-MB MAX reagent kit (DNA Technology, Moscow). The extracted DNA was stored in –40 °C prior to polymerase chain reaction (PCR). PCR was performed using a DT Prime amplifier (DNA Technology, Moscow) in accordance with the manufacturer's user manual. The number of target DNA copies (lg10) in the sample was calculated using the threshold cycle comparison method, also known as the $\Delta\Delta C_T$ method [15].

The DNA samples were analyzed by multiplex real-time PCR using Femoflor®16 and BacScreen OM reagent kits (DNA Technology, Moscow). Both tests are based on multiplex real-time PCR, which allows to determine the amount of DNA of the sought microorganism in a sample, expressed in genome equivalents. The quantity of genome equivalents is proportional to the number of microorganism cells. Femoflor®16 test is used to determine the concentration of bacterial DNA — total bacterial mass (TBM). The detailed description of each test is available within our previous publication [12].

Bias

Several measures were taken to reduce potential bias. Participants received standardized instructions for urine collection to minimize contamination. Urethral and vaginal specimens were collected according to a standard procedure. The same laboratory workflow was used for all groups. Nevertheless, contamination of voided urine samples, personnel variation in swab sampling, and residual confounding could not be fully excluded

Study size

No formal a priori sample size calculation was performed. The study to the exploratory nature of the study, the final sample size was determined by the number of eligible women recruited during the predefined study period. Overall, 150 participants were enrolled.

Quantitative variables

Quantitative PCR-derived variables were analyzed as logarithmic values where applicable. For microbiota composition analyses, the abundance of individual taxa or bacterial groups was normalized to TBM and expressed as a percentage of the total bacterial signal. For the reason that the distributions were anomalous, continuous variables were summarized using medians and interquartile ranges.

Statistical methods

Statistical analysis was performed using IBM SPSS Statistics version 29 for Windows (IBM, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test, which showed no normal distribution of the analyzed data. The Mann–Whitney *U*-test was used to analyze the differences between the groups.

Results

Quantitative characteristics of the specimens across the study groups

A total of 150 participants met the eligibility criteria for this study. Out of them, 34 healthy volunteers were in the "Control" group, 16 participants were in the "Risk of UTI" group, and 100 patients were in the "rLUTI" group.

The quantitative assessment of the specimens showed differences in the overall microbial characteristics across the study groups. The data presented

Table 1. Genomic DNA levels in participants

Type specimen	Control *n* = 34	Risk of UTI *n* = 16	rLUTI *n* = 100
Midstream urine	0.0 (0.0;3.4)	3.3 (0.8;3.8)*	4.0 (3.3;4.9)#
First-pass urine	3.5 (0.0;4.0)	4.0 (3.6;4.1)*	4.4 (3.6;5.1)#
Urethral swab	4.1 (3.7;4.4)	4.2 (3.7;4.3)	4.1 (3.7;4.5) (*n* = 99)
Vaginal swab	4.9 (4.4;5.2)	4.6 (4.5;5.2)	4.9 (4.6;5.2) (*n* = 98)

Note: values are presented as median (*Q*1; *Q*3) of logarithmic values; * – $p < 0.05$ compared with "Control"; # – $p < 0.001$ compared with "Control". Pairwise comparisons were performed using the Mann–Whitney *U* test.

Table 2. Levels of total bacterial mass in participants

Type specimen	Control *n* = 34	Risk of UTI *n* = 16	rLUTI *n* = 100
Midstream urine	5.1 (3.7;6.0)	6.1 (5.2;6.7)*	6.8 (5.1;8.1)#
First-pass urine	5.7 (4.4;6.6)	6.2 (5.7;7.4)*	6.8 (5.9;8.1)#
Urethral swab	5.3 (4.6;6.0)	5.1 (4.6;5.8)	5.1 (4.5;5.9) (*n* = 99)
Vaginal swab	6.9 (6.6;7.3)	6.8 (6.5;7.4)	6.8 (6.2;7.2) (*n* = 98)

Note: values are presented as median (*Q*1; *Q*3) of logarithmic values; * – $p < 0.05$ compared with "Control"; # – $p < 0.001$ compared with "Control". Pairwise comparisons were performed using the Mann–Whitney *U* test.

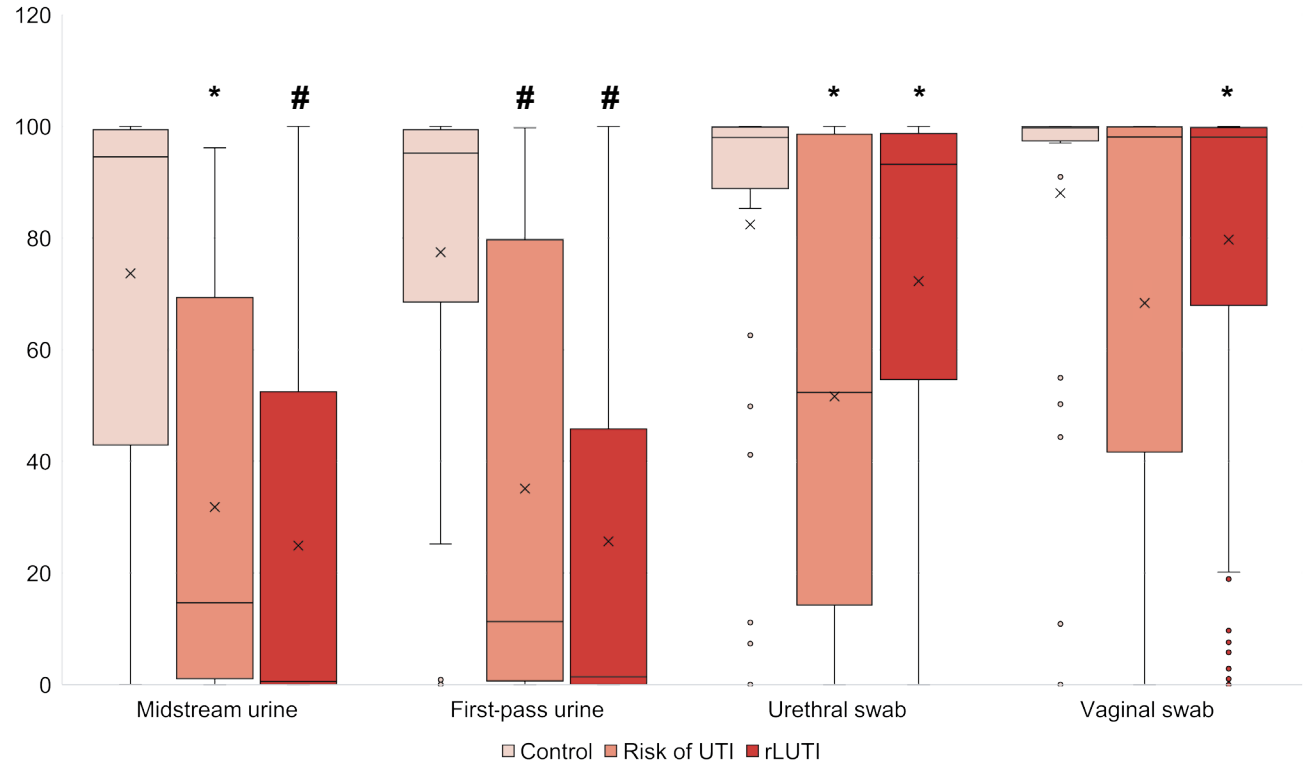
show an increase in genomic DNA and bacterial quantities in patients with rLUTI as well as in patients with microlithiasis and/or BV compared to healthy controls, but only in midstream and first-pass urine samples. No differences were observed in urethral and vaginal swabs between the study groups. The quantitative values of genomic DNA and TBM for the midstream urine, urethral swabs, and vaginal swabs are presented in Tables 1 and 2.

Site-specific microbiota composition in urine, urethral, and vaginal samples

A detailed comparison of the participants' microbiota was then performed. The microbiota was compared between the studied groups based on the number of bacteria/bacterial groups normalized to the TBM for each biotope.

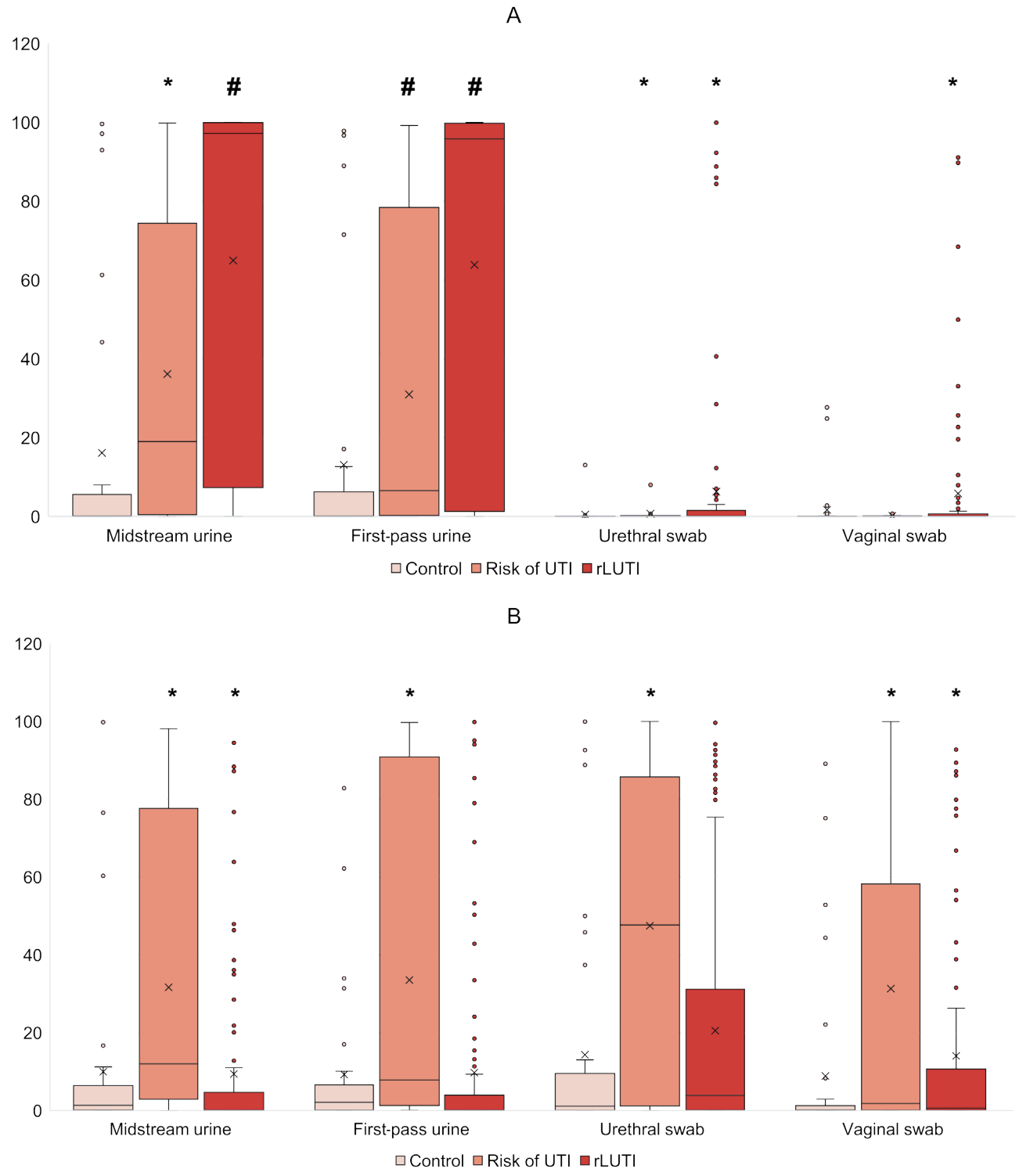
The relative presence of LB, a major contributor to urogenital normobiota in women, was critically reduced in both urine samples in patients with rLUTI compared with healthy volunteers. In patients with rLUTI, LB levels were slightly but statistically significantly reduced in urethral and vaginal swabs compared with in the "Control" group ($p = 0.022$ and $p = 0.008$, respectively). A decrease in relative LB levels was observed in the urethral swabs of patients with risk of UTI, compared with in the "Control" group ($p = 0.024$). Their vaginal swabs also showed a decrease in LB compared with the "Control" group, but the difference was not statistically significant ($p = 0.086$), but only in a minority of patients. Relative levels of *Lactobacillus* spp. in midstream urine, first-pass urine samples and urethral, vaginal swabs of participants are presented in Figure 1.

FIG. 1. *Lactobacilli* proportion in different samples



Note: relative levels of *Lactobacillus* spp. are presented as percentages of the total bacterial mass. "Control" group, $n = 34$ for all types of specimens; "Risk of UTI" group, $n = 16$ for all types of specimens; "rLUTI" group, $n = 98$ for first-pass urine, vaginal swab and urethral swab, $n = 100$ for midstream urine.
* – $p < 0.05$ compared with "Control"; # – $p < 0.001$ compared with "Control". Pairwise comparisons were performed using the Mann–Whitney *U* test.

FIG. 2. Type of microorganism proportion in different samples



Note: data are presented as median (*Q*1; *Q*3). Relative levels of facultative and obligate anaerobic microorganisms are expressed as percentages of the total bacterial mass. "Control" group, *n* = 34 for all types of specimens; "Risk of UTI" group, *n* = 16 for all types of specimens; "rLUTI" group, *n* = 97 for urethral swab, *n* = 98 for first-pass urine and vaginal swab, *n* = 100 for midstream urine. Pairwise comparisons were performed using the Mann–Whitney *U* test; * — $p < 0.05$ compared with "Control"; # — $p < 0.001$ compared with "Control"; A — Facultative anaerobic microorganisms in different samples (%); B — Obligate anaerobic microorganisms (%).

The relative LB quantities were also reduced in patients with risk of UTI in both urine portions, but to a lesser extent compared to patients with rLUTI. The normalized values for the midstream urine, first-pass urine samples, urethral and vaginal swabs are presented in Supplementary Tables 1–4, respectively (supplementary materials on the journal website https://doi.org/10.47093/3033-5493.2026.2.1.57-68-annex).

The decrease in the relative quantities of LB was accompanied by an increase in other bacteria/bacterial groups. Figures 2A and 2B present comparative plots of the relative quantities of total facultative and obligate anaerobic microorganisms in all studied groups.

In patients with rLUTI, both urine portions were dominated by facultative anaerobes, primarily bacteria of the order The predominance of *Enterobacterales* was accompanied by a significant decrease in *Lactobacillus* spp. in both urine portions ($p < 0.001$). Among the other bacterial groups, significant differences from healthy controls were limited to *Lachnobacterium* spp./*Clostridium* spp. and *Mobiluncus* spp./*Corynebacterium* spp. in both urine samples, with an additional significant difference in *Staphylococcus* spp. in first-pass urine. Thus, the main microbiological pattern in patients with rLUTI was the marked replacement of lactobacilli by *Enterobacterales*-dominated facultative anaerobic microbiota.

In the "Risk of UTI" group, a decrease in urinary LB level was associated with an increase in both facultative and obligate anaerobes. In both urine samples, facultative anaerobes were represented by the order *Enterobacterales*, while obligate anaerobes comprised of *Gardnerella vaginalis*/*Prevotella bivia*/*Porphyromonas* spp., *Eubacterium* spp., *Sneathia* spp./*Leptotrichia* spp./*Fusobacterium* spp., *Megasphaera* spp./*Veillonella* spp./*Dialister* spp., *Peptostreptococcus* spp., *Atopobium vaginae.* At the same time, a decrease in LB in the urethral swabs was linked to an increase in obligate anaerobic microbiota, in contrast to healthy volunteers ($p = 0.011$). The representation of anaerobic microorganisms was almost the same as in urine samples (Supplementary Tables 1, 2). In vaginal swabs, a decrease in lactobacilli was also accompanied by an increase in anaerobic microbiota of the similar spectrum in a small proportion of patients (Supplementary Tables 3, 4).

Discussion

In the present study, the composition of microbiota of first-pass and midstream urine, urethral and vaginal mucosa in women was investigated by real-time PCR to evaluate the association between urinary tract infections and the microbiota of different biotopes of the urogenital tract. In our previous study [12] we have shown that for midstream urine sample, the biomaterial traditionally used for diagnosing cystitis, qualitative classification (AUC = 0.88 (0.81; 0.95)) of patients with rLUTI and healthy controls is based on three main indicators: the amount of genomic DNA originating from human epithelial cells and leukocytes, TBM, and the proportion of LB in the total bacterial count. Therefore, the present study employed the same indicators for other biotopes as well.

In patients of "rLUTI" group, the amount of genomic DNA in midstream and first-pass urine samples significantly increased in comparison to the "Control" group. At the same time, no differences were observed in the urethral and vaginal swabs between patients with rLUTI and healthy volunteers. It should, however, be noted that the quantity of genomic DNA in a swab depends on an external factor: the biomaterial is collected by a doctor. The amount of

genomic DNA in freely released urine is less dependent on external factors, so this indicator is more objective, and perhaps it can be used as a laboratory criterion for inflammation in the urinary tract, which is standardly assessed based on the number of epithelial cells and leukocytes in the urinalysis [16, 17]. However, within current trial we did not assess such correlation. The absence of significant differences in urethral and vaginal swabs between patients of "rLUTI" group and healthy volunteers may also be explained by the dependence of swab-based quantitative results on the technique of material collection.

TBM is an indicator of bacterial quantity in a sample [18]. In patients of "rLUTI" group, it was significantly higher than in the "Control" group in both urine samples. However, in the urethral and vaginal swabs, the bacterial quantities did not differ between patients from all groups. The same pattern is true for genomic DNA, which may reflect the dependence of the quantitative result of scraping on the technique of material collection.

Our findings support the view that the ratios between opportunistic and normobiotic bacteria may be more informative for assessing microbiota disorders than their quantitative values. Han et al. also reported on the importance of maintaining a balance between the normal microbiota and opportunistic/anaerobic bacteria in the development of gynecological diseases, including inflammatory conditions [19]. Normalizing particular species or groups of bacteria to the total bacterial quantity, i.e. calculating the proportion of a specific microorganism or a group of microorganisms in the TBM of a sample, provides such a possibility. Additionally, normalization to the TBM makes it possible to compare the microbiota from biomaterial specimens obtained using different methods, including swabs and free-flowing urine.

Thus, the relative quantity of LB, the main component of urogenital normobiota in women [20, 21], was critically reduced in both the midstream and first-pass urine samples in patients with rLUTI as compared to healthy controls. The levels of LB were also reduced in urethral and vaginal swabs, but in a very small fraction of patients. This decrease was less pronounced in swabs than in urine samples.

A decrease in LB has to be associated with increased levels of other bacteria. The main question is, "What other bacteria have so significantly 'edged out' lactobacilli in patients with rLUTI?" In both the midstream and first-pass urine samples of these patients, facultative anaerobes were dominant, with almost all of them belonging to the order *Enterobacterales*. This pattern reflected a significant decrease in *Lactobacillus* spp. and a significant increase in *Enterobacterales*-dominated facultative anaerobic microbiota compared with healthy controls. Among the other bacterial groups, significant differences from controls were limited to *Lachnobacterium* spp./*Clostridium* spp. and *Mobiluncus* spp./*Corynebacterium* spp. in both urine samples, with an additional significant difference in *Staphylococcus* spp. in first-pass urine. Conducted results support the concept that rLUTI is not necessarily limited to the predominance of one uropathogen, but may reflect a broader urogenital dysbiosis. This is also in line with previous studies in which the urinary microbiota of women with recurrent UTI/recurrent cystitis differed from that of controls, including shifts in *Lactobacillus*, *Enterobacterales*, and *Escherichia*/*Shigella* [22, 23].

Lewis et al. analyzing the relationship between vaginal microbiota and UTI suggested that "vaginal bacteria may cause UTI, either themselves (i.e. a traditional uropathogen using the vagina as a reservoir) or by acting as a 'covert pathogens' to facilitate pathogenesis of another organism" [2]. In the present study, analysis of the microbiota of urine, urethral and vaginal swabs of patients with rLUTI showed that a variant of UTI without evident involvement

of the vaginal biotope is possible. Perhaps the described variant of UTI with a significantly altered urinary microbiota and a completely normal vaginal microbiota in patients of "rLUTI" group is a variant of the course of UTI, or it can be a stage of disease progression.

Patients in "Risk of UTI" group had no evident symptoms of urinary infections, but they were not included in the healthy "Control" group due to having microlithiasis and/or BV as a diagnosis. Since both BV and stone formation have been associated with abnormalities of the urinary tract microbiota [24–26], we deemed it reasonable to include these women in the study as a separate group of patients, whom we considered 'neither obviously ill nor healthy'.

The microbiota profile of patients in the "Risk of UTI" group can be considered as an intermediate variant between healthy volunteers and patients of "rLUTI" group. Although these women had no evident symptoms of urinary tract infection, their urine samples showed higher genomic DNA and TBM values, together with a decrease in urinary LB, compared with healthy controls. The decrease urinary lactobacilli was linked to an increase in both facultative and obligate anaerobes, in approximately equal proportions. Facultative anaerobes were represented by *Enterobacterales*, while obligate anaerobes mainly constituted of microorganisms associated with BV [27, 28]. In contrast to patients with recurrent lower urinary tract infection, in whom LB were dominant in urethral and vaginal swabs, in patients with urolithiasis and/or BV the proportion of LB in urethral swabs was reduced in some patients [29, 30]. Thus, urinary and urethral microbiota alterations may be detected even when vaginal dysbiosis is not clearly expressed, although in cases where lactobacilli were reduced in the urethra and vagina, this decrease was accompanied by an increase in a similar spectrum of anaerobic microbiota associated with BV.

A limitation of this study is clearly the small group size and heterogeneity of patients with BV and/or urolithiasis, which makes it difficult to reach definitive conclusions. Nevertheless, the obtained results suggesting that decreased lactobacilli and increased BV-associated anaerobic microbiota in urine and urinary tract mucosa in the absence of clinical UTI signs may partially support the hypothesis that BV-associated organisms may play an important role in the etiology of uropathology and uropathogenesis. However, more studies are needed to determine the causal role of these organisms in the development of symptomatic UTI.

Undoubtedly, larger sample sizes are needed for a study with more specific grouping. The use of the presented research tools is promising. Future studies may be able to identify combinations of pathotype variants of the urinary and genital microbiota in different variants/stages of disease, which, in turn, would allow the development of more specialized approaches to treatment and prevention of urinary infections.

Another potential limitation is possible contamination of the specimens. Obtaining urine with a catheter might reduce it, but we decided to avoid this invasive test. In order to standardize the procedure of specimen collection, patients were instructed in detail how to perform it properly.

Conclusion

Analyzing biomaterial samples from different segments of the urogenital tract provides a comprehensive approach to studying and diagnosing UTI. Analysis of midstream and first-pass urine samples yielded similar results, suggesting that both samples can be reliably used to determine the presence

of inflammation in the urogenital tract. At the same time, the findings from the urethral and vaginal swabs reveal a different pattern. For instance, comparing the vaginal and urinary microbiota of patients of "rLUTI" group to showed that UTI do not necessarily affect the vaginal biotope. The swabs, however, appear to be less objective as a diagnostic tool due to being dependent on the quality of the swab itself. Thus, the presented data may serve as supporting evidence when selecting the type of specimen for microbiological assessment in the diagnosis of UTI.

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Regenerative Medicine

Mini-Review

Therapeutic potential of mesenchymal stromal cell-derived extracellular vesicles in obstetrics and gynecology

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ABSTRACT

In recent years, mesenchymal stromal cell (MSC) therapy has been widely studied as a major trend in medicine. However, it faces several clinical limitations, including immune reactions, tumor risks, and low homing efficiency. Consequently, cell-

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free strategies using MSC-derived extracellular vesicles (MSC-EV), particularly exosomes, are being studied as an increasingly recognized safer alternative. This mini-review aims to summarize current preclinical and early clinical evidence on the therapeutic potential of MSC-EV in female reproductive disorders, with a particular focus on premature ovarian insufficiency and thin endometrium, and to outline the key translational challenges to their clinical application.

Preclinical and clinical data indicate that MSC-EV modify target tissue functions by transferring microRNA, proteins, and lipids. In chemotherapy-induced premature ovarian insufficiency models, MSC-EV restore folliculogenesis, increase anti-Müllerian hormone levels, and reduce granulosa cell apoptosis. In thin endometrium models, vesicles improve tissue regeneration and stimulate angiogenesis via the wingless-related integration site / β-catenin and mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) pathway. Overall, MSC-EV serve as a viable cell-free option in reproductive medicine, though standardized protocols and robust clinical trials are still required.

Key Words: regenerative gynecology; exosomes; mesenchymal stromal cells; female infertility; premature ovarian insufficiency; diminished ovarian reserve; thin endometrium

MeSH terms:
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Introduction

The management of reproductive disorders, such as premature ovarian insufficiency (POI) and refractory thin endometrium, remains a clinical challenge due to their complex etiologies and association with female infertility. Over the past decade, regenerative medicine has introduced approaches ranging from whole-cell therapies to cell-free exosome-based strategies [1].

In preclinical models, mesenchymal stromal cell (MSC) transplantation demonstrates clear therapeutic effects. In a chemotherapy-induced POI model, Park et al. reported first-cycle pregnancy rates of 60–100% depending on dose, with fertility maintained at 60–80% in subsequent cycles [2]. MSC also increase endometrial thickness and enhance receptivity [1]. However, direct MSC transplantation has notable limitations: donor variability, immune reactions, tumor risks, low in vivo survival, and embolization risks during systemic administration. Cryopreservation, standardization, and transport of live cells are logistically difficult [3]. These challenges have shifted focus toward cell-free alternatives, specifically MSC-derived extracellular vesicles (MSC-EV), which retain parental cell therapeutic properties with enhanced safety and stability [1, 3].

To date, most available reviews have usually considered either mesenchymal stromal cells or MSC-EV separately. As a result, they only rarely offer a direct and clinically relevant comparison between whole-cell and cell-free approaches, especially in the context of premature ovarian insufficiency and thin endometrium [3, 4]. This mini-review tries to address this gap. It

summarizes recent preclinical evidence and the first clinical data on MSC-EV in female infertility and also compares MSC and MSC-EV in terms of their efficacy, duration of effect, safety profile, and practical potential for clinical translation.

This review aims to critically compare the therapeutic potential and limitations of whole-cell MSC versus MSC-EV in female fertility restoration, to synthesize the current preclinical and clinical evidence on MSC-EV efficacy, and to outline the key translational challenges that must be addressed before clinical adoption. We reviewed original articles and clinical trials (2018–2025) identified through PubMed and Web of Science using keywords: “extracellular vesicles”, “exosomes”, “mesenchymal stromal cells”, “female infertility”, “premature ovarian insufficiency”, “diminished ovarian reserve”, “thin endometrium”.

Mesenchymal stromal cells and their derived extracellular vesicles: a comparison of therapeutic characteristics

Extracellular vesicles (EV), including exosomes (30–150 nm) and microvesicles (100–1000 nm), mediate intercellular communication by transferring regulatory non-coding RNA (microRNA and long non-coding RNA), bioactive proteins, cytokines, and lipids [1]. Upon endocytosis, membrane fusion, or receptor binding, their cargo modulates target cell signaling. Therapeutic effects rely on paracrine regulation driving three core processes:

- Anti-apoptosis: MSC-EV mediate protective effects by modulating signaling pathways involved in cell survival and inhibiting pro-apoptotic cascades [5–7]. By regulating the balance of pro- and anti-apoptotic proteins, MSC-EV inhibit programmed cell death and promote tissue repair in reproductive models [6, 7].
- Angiogenesis: MSC-EV promote the formation of new microvascular networks by delivering bioactive cargo that stimulates endothelial cell proliferation, migration, and tube formation [8, 9]. Research indicates that the angiogenic capacity of these vesicles is influenced by the tissue source of the parental MSC, as well as the environmental conditions — such as hypoxia — during vesicle production, which enhance their ability to drive functional angiogenesis in damaged tissues [8, 9].
- Immunomodulation: macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype reduces tumor necrosis factor-α and interleukin (IL)-1β while increasing IL-10 and transforming growth factor-β [10].

Through these molecular mechanisms, MSC-EV reduce inflammation and apoptosis in ovarian tissue [3], while promoting angiogenesis and inhibiting fibrotic growth in endometrial dysfunction models [1]. However, their efficacy can be limited compared to whole-cell therapy. For instance, in the aforementioned study, Park et al. reported first-cycle pregnancy rates of 30–50% in the exosome group, with no pregnancies in subsequent cycles, whereas whole-cell MSC provided sustained effects [2].

Key advantages of MSC-EV include absence of nucleus, eliminating genetic integration and minimizing tumor risk, and low immunogenicity facilitating standardization and storage. Unresolved challenges include the lack of unified isolation and quality assessment protocols, complicating cross-study comparisons [3]. Ultimately, MSC and MSC-EV are complementary:

whole-cell therapy offers more sustained functional effects [2], while cell-free approaches provide superior safety and producibility [3]. The key differences between whole-cell MSC therapy and MSC-EV therapy are summarized in Table 1.

We conclude that neither modality is universally superior; rather, MSC and MSC-EV occupy distinct therapeutic niches defined by the trade-off between efficacy durability and safety.

Preclinical efficacy of mesenchymal stromal cell-derived extracellular vesicles

Animal models demonstrate efficacy of MSC-EV derived from various tissues, including human umbilical cord MSC-EV (hUC-MSC-EV) and brown adipose tissue, in polycystic ovary syndrome, POI, and implantation failure (e.g., thin endometrium) [6].

Zhang et al. showed that brown adipose tissue-derived exosomes restore oocyte mitochondrial activity, increase primordial, secondary, and antral follicle counts, and increase litter sizes in aging mice [11]. In chemotherapy-induced POI models, Xiao et al. reported that hUC-MSC-EV minimize DNA double-strand breaks, increase the Bcl-2/Bax ratio, suppress granulosa cell apoptosis, and down-regulate IL-1β and IL-6 [7]. Ding et al. demonstrated that engineered hUC-MSC-EV carrying a phosphatidylinositol 3-kinase / protein kinase B / mammalian target of rapamycin (PI3K/Akt/mTOR) agonist restore the estrous cycle and reduce cystic follicles in polycystic ovary syndrome models, outperforming unmodified vesicles [12].

For endometrial applications, Lin et al. reported that an EV-enriched biocompatible hydrogel promotes endometrial repair, increases functional layer thickness, stimulates angiogenesis, and enables live births in rats with endometrial injury [13].

Beyond therapy, follicular fluid EV serve diagnostic roles. Hu et al. identified exosomal microRNA profiles correlating with follicle size and maturity, targeting follicle-stimulating hormone secretion and transforming growth factor-β pathways, suggesting utility as non-invasive biomarkers of oocyte competence [14].

Collectively, these preclinical data establish a robust mechanistic foundation for MSC-EV therapy across distinct reproductive pathologies. However, we note that the marked efficacy observed in homogeneous animal models must be interpreted cautiously, as human populations present far greater biological and etiological heterogeneity.

Table 1. comparative characteristics of whole-cell mesenchymal stromal cell and mesenchymal stromal cell-derived extracellular vesicles

Characteristic	Whole-cell mesenchymal stromal cells	Mesenchymal stromal cell-derived extracellular vesicles
Therapeutic mechanism	Paracrine secretion with possible cellular persistence	Paracrine regulation (proteins, lipids)
Tumor risk	Potential risk	Low/minimal (acellular)
Immunogenicity	Variable	Low
Stability/storage	Difficult (requires cryopreservation)	High (stable, easier to store/transport)
Efficacy profile	Sustained functional effects	Transient (often requires repeated dosing)
Standardization	Complex (donor variability)	More feasible than cell therapy

Clinical efficacy of mesenchymal stromal cell-derived extracellular vesicles and related extracellular vesicle-based therapies

Therapeutic effects of extracellular vesicles in endometrial pathology

While extensive preclinical data demonstrate promising regenerative effects of MSC-EV, the study by Ebrahimi et al. stands as a primary published clinical trial [15]. In this single-center randomized controlled trial the authors evaluated the effectiveness of intrauterine injection of placental MSC-EV in women with persistent thin endometrium during frozen embryo transfer cycles. By the transfer day, women treated with exosomes demonstrated a higher mean increase in endometrial thickness, but this difference was not statistically significant. However, MSC-EV administration was associated with fewer cycle cancellations due to insufficient endometrial response. Clinical pregnancy rates were 12.5% for women treated with exosomes and 6.6% among those who did not receive this intervention. No adverse events were reported [15].

Although these results did not reach statistical significance for the primary endpoint, the clinically meaningful reduction in cycle cancellations and the numerically higher pregnancy rates suggest a promising signal that warrants confirmation in larger multicenter trials.

Therapeutic effect of extracellular vesicles in ovarian dysfunction

Ovarian dysfunction studies are currently limited to pilot trials and case reports, with a growing number of clinical investigations evaluating the efficacy of diverse EV-based therapeutic strategies [16–19]. Navarro et al. conducted a prospective randomized study comparing the intraovarian administration of autologous plasma-derived EV, platelet-rich plasma, and saline in women with diminished ovarian reserve [16]. Plasma-derived EV therapy was associated with improved ovarian reserve parameters, including follicle-stimulating hormone, luteinizing hormone, estradiol, anti-Müllerian hormone, and antral follicle counts, as well as enhanced reproductive outcomes, such as a higher number of metaphase II oocytes, elevated fertilization rates, and higher clinical pregnancy rates [16].

Complementing these findings, evidence from early clinical studies discussed in the reviews has further characterized the therapeutic potential of MSC-EV [18, 19]. Moustaki et al. emphasize in their comprehensive review that cell-free biological therapies, particularly exosomes, offer a promising non-hormonal approach to rejuvenating the ovarian microenvironment and supporting follicular viability [19]. Furthermore, Geng et al. provided evidence that EV administration could modulate the local ovarian microenvironment, potentially overcoming resistance to conventional hormonal stimulation [18]. Alongside these trials, the clinical feasibility of local autologous EV delivery is supported by case report, including a documented spontaneous pregnancy following the intraovarian injection of menstrual blood-derived exosomes in a patient previously unresponsive to standard stimulation protocols [17].

While these preliminary findings are highly encouraging due to their favorable safety profile, the current evidence base remains restricted to small-scale pilot studies. Consequently, these data are currently insufficient to support broad clinical recommendations, and further validation in larger, multi-center randomized controlled trials is essential to establish the durability of these effects and standardize dosing regimens.

Prospects and challenges for mesenchymal stromal cell-derived extracellular vesicles therapy

Currently, MSC-EV should be considered as an alternative or adjunct to whole-cell MSC transplantation rather than a complete replacement [3]. While cell-free approaches avoid cellular therapy risks and provide non-hormonal, organ-preserving options in gynecology [1, 3], clinical evidence remains limited. To date, no Phase III randomized controlled trials have been published; available data are restricted to preclinical models, pilot Phase I/II studies, and clinical registries [6]. Standardized trials are required to establish predictable outcomes before MSC-EV can be translated into routine clinical practice.

In our view, the path to clinical translation hinges on resolving three interconnected challenges: the standardization of isolation and characterization protocols, the establishment of disease-specific dosing regimens, and the execution of adequately powered randomized trials. Until these milestones are achieved, MSC-EV will remain a promising but experimental modality.

Conclusion

The reviewed evidence highlights the role of EV in modulating reproductive physiology and underscores their dual utility as non-invasive diagnostic tools and promising therapeutic agents for fertility disorders. While the preclinical rationale is compelling and early clinical signals are encouraging, we conclude that the field has not yet crossed the threshold from experimental promise to evidence-based practice. Concerted efforts toward standardization and rigorous clinical evaluation will determine whether MSC-EV fulfill their therapeutic potential in reproductive medicine.

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Notes