PROCEEDINGS OF

SOCRATIC LECTURES

PART II: MEDICINE

14TH INTERNATIONAL SYMPOSIUM, LJUBLJANA, APRIL 17, 2026

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14th International Symposium, Ljubljana, April 17, 2026

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The members of the Organizing Committee of 14th Socratic Lectures: Jelen Andreja, Mojca Amon, Tamas Beke Somfai, Mariapia Borghesan, Aleksandra Drozdf-Rzoska, Nelson Gomes, Aleš Iglič, Yelena Istileulova, Jošt Janša, Alfredo Juan, Samo Kralj, Veronika Kralj-Iglič, Daniel Manoso-Hernando, Gabriella Pocsfalvi, Lilla Turiak, Olga Sebestova Janouskova, Blaž Švajger, Gregory Papanikos, Renata Vauhnik.

Program of the Symposium Socratic Lectures, April 17, 2026, 10:00 – 17:00 (Ljubljana time)

10.00 Welcome to participants: Veronika Kralj-Iglič

10.10 - 10.45 Plenary lecture: Sebestova Janouskova Olga: Extracellular Vesicles: nanosize natural particles with BIG biological impact

11.00 Scientific sections

Section 1: Medicine (Chairs Amon Mojca, Janša Jošt)

11.00 - 11.30 Kneževič Ivan: From Bedside to Bench: Translating Clinical Needs into Next-Generation Regenerative Biomaterials
11.30 - 11.45 Jelenc Matija: Preoperative Planning of Aortic Valve Repair in Cardiac Surgery
11.45 - 12.00 Janša Jošt, Amon Mojca, Hawlina Simob: Beyond Tumour Biology: The Role of Body Composition in Risk Stratification of NMIBC Surgery
12.00 - 12.15 Trotovšek Blaž, Serša Gregor, Đokić Mihajlo: Electrochemotherapy - From Lab to Clinics
12.15 - 12.30 Kšela Juš, Racman Mark: Environmental Determinants of Cardiovascular Disease: Integrating Air Pollution, Metal Exposure, and Early Vascular Pathology
12.30 - 12.45 Amon Mojca: Exercise Physiology and Ergonomics – Bridging Physiological Extremes to Pathology
12.45 - 13.00 Kreča Žak, Strajnar Jan, Poredoš Jana, Nikolov Žan, Mali Katra, Boc Anja: Upper limb mobility after breast cancer surgery: pathoanatomical changes and šhysiotherapy approaches

Section 2 : Biomedicine (Chair Vauhnik Renata, Manoso-Hernando Daniel)

11:00 Keynote lecture: Manoso-Hernando Daniel, Mateo-Quel Jesús, Villaverde-Rúa Mario, Fernández-Llamazares-Mateos Gabriel: Comparison of shoulder muscle activation and strength between sides during the Closed Kinetic Chain Upper Extremity Stability Test and its modified version in patients with rotator cuff–related shoulder pain
11:30 - 11:45 Jelen Matic, Weber Daša, Kejžar Nataša, Vauhnik Renata: Correlation of Knee Joint Stabilization Force With Anterior and Mediolateral Rotational Laxity Using the Dyneelax Arthrometer
11:45 - 12:00 Breznik Katarina, Potočnik Maja Marija, Vauhnik Renata, Frangež Maja: Electrical potential of the deep abdominal muscles during different exhalation techniques
12:00 - 12:15 Fijavž Staš, Jerebic Mark, Milaković Rina, Olip Nejc, Paladin Maša, Žager Marciuš Valerija, Gošnak Dahmane Raja: The role of radiation therapists in addressing the side effects of radiation exposure
12:15 - 12:30 Strnad Špela, Jevsnik Podlesnik Mojca, Jamnikar-Ciglenecki Urska: Short Food Supply Chains in Slovenia: Main Challenges and Future Growth
12:30 - 12:45 Ančimer Špela, Antončič Jerca, Hrovatin Ajda, Pilih Klemen Aleš, Vauhnik Renata: Medial discoid meniscus treated with platelet-rich plasma: A case report
12:45 - 13:00 Vovk Lara, Vauhnik Renata: Physiotherapy approach in linear scleroderma of the lower limb: A case report

Section 3: Extracellular particles (Chair Pocsfalvi Gabriella, Turiak Lilla)

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11:25 - 11:50 Keynote lecture: Ambrosone Alfredo: Exploring Plant Extracellular Vesicles for Innovative bio-based therapies
11:50 - 12:00 Chang Yu-Hsin: µPulse TFF optimization for plant-derived extracellular vesicle isolation
12:00 - 12:10 Patil Pradnya, Pratiwi Feby, Tokarchuk Kateryna, Oh JaeWon, Kim Kwang Pyo, Vainio Seppo: Comparative Proteomic Analysis of Strawberry-Derived Nanovesicles and Total Protein Extracts from Biodynamic and Conventional Strawberries
12:10 - 12:20 Moubarak Maneea: Plant tissue culture
12:20 - 12:30 Bautista Hernandez Olivia del Carmen: From Cells to Cytokines: A Microfluidic Approach to Study Anti Inflammatory Effects of Plant-Derived Nanovesicles

12:30 - 12:40 Kralj- Iglič Veronika, Romolo Anna, Istileulova Yelena, Iglič Aleš: Coacervation: a mechanism of extracellular particle formation
12:40 - 12:50 Murto Henri: EV lab on a farm and new possibilities of regenerative farming for circular economy

12:50 Discussion

Section 4: Biophysics (Chairs Iglič Aleš, Beke Somfai Tamas

11:00 - 11:30 Keynote lecture: Beke Somfai Tamas: Supramolecular antibiotics killing Gram-negative bacteria by mechanical membrane damage
11:30 - 11:45 Mercaldo Beatrice, Anna Romolo, Matej Hočevar, Matic Kisovec, Apolonija Bedina Zavec, Boštjan Korenjak, Aleš Iglič, Antonio DiLoria, Veronika Kralj-Iglič: Measuring density and viscosity of samples as an improvement of interferometric light microscopy
11:45 - 12:00 Arko Matevž, Matej Hočevar, Boštjan Korenjak, Iglič Aleš, Kralj-Iglič Veronika: Extracellular particles from equine and bovine milk
12:00 - 12:15 Korenjak Boštjan, Romolo Anna, Tratenšek Armando, Nemec Svete Alenka, Drobne David, Aleš Iglič, Vladimira Erjavec, Veronika Kralj-Iglič: Comparison of extracellular vesicle characteristics of human and dog
12:15 - 12:30 Mesarec Luka, Kralj-Iglič Veronika, Kralj-Samo, Iglič Aleš: Effect of the concentration of curved rod-like molecules on the equilibrium shapes of two-dimensional shells
12:30 - 12:45 Drab Mitja: Modeling active anisotropic membrane inclusions
12:45 - 13:00 Klemenc Ana: Applications of surface-enhanced Raman spectroscopy in biomedicine

Section 5: Materials (Chairs Kralj-Iglič Veronika, Juan Alfredo)

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11:30 - 11:45 Bar Laure, Lavrič Marta, Caf Maja, Kralj Slavko, Kumar Sadhu Raj, Škarabot Miha, Losada-Pérez Patricia, Iglič Aleš, Cordoyiannis George: Lipid-phase-modulated interactions of gold nanoparticles with supported vesicular membranes
11:45 - 12:00 Cepec Eva, Godič Torkar Karmen, Šunta Urška, Griessler Bulc Tjaša, Manjarres Castro June, Istenič Darja: The Microbial Comeback: Challenges in Achieving Long-Term Axenic Microalgal Cultures
12:00 - 12:15 Bosković Neda: Microplastics in aquatic environment: insight from research in Montenegro
12:15 - 12:30 Karas Tjaša: Applications of Machine Learning in Brillouin Spectroscopy
12:30 - 12:45 Žarkovič Lara, Zupan Iza, Hankić Larisa, Žager Marciuš Valerija, Gošnak Dahmane Raja: Patient Safety in Radiotherapy: Human Factors and Error Prevention Systems
12.45 - 13:00 Bensa Maja, Jevšnik Podlesnik Mojca, Vovk Irena: Consumers' food safety concerns in a changing food landscape

Section 6: Complexity (Chairs Jelen Andreja and Švajger Blaž)

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11:30 - 11:45 Jelen Andreja: Formation of complex patterns in Ferromagnetic High-Entropy Alloys which leads to magnetic softness
11:45 - 12:00 Župec Matjaž: Power-law and Tsallis distribution in football goal scoring
12:00 - 12:15 Sgerm Jaka, Kodrin Marcel: Visualising order parameter spaces
12:15 - 12:30 Dovnik Damjan: Quantum Hall Effect
12:30 - 12:45 Fras Rene: Electrocaloric effect
12:45 - 13:00 Michelini Sara, Bele Marjan, Tatti Francesco, Drobne Damjana, Mandič Mulec Ines, Šimunovič Katarina: Influence of in vitro model complexity on Campylobacter jejuni–host interactions

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11:30 - 11:45 Melani Potrč: Dynamic Light Scattering as a Tool for Characterization of DNA-quadruplexes
11:45 - 12:00 Javornik Tim, Kravos Iztok: Kibble Zurek Mechanism in Confined Geometries

12:00 - 12:15 Zid Maha: Topological charge conservation in planar confinements
12:15 - 12:30 Hölbl Arbresha: Weakly disordered soft matter
12:30 - 12:45 Ribaš Anja: Chaotic Metasurfaces
12:45 - 13:00 Švajger Blaž: Percolation in electrocaloric applications

Section 8: Artificial Intelligence in the Classroom – Partner or Challenge? and STEAM as a Catalyst for Educational Innovation (Chairs Gomes Nelson and Borghesan Mariapia)

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11:15 - 11:25 Brogna Daniela: STEAM Hackathon: Sky patterns on the ceramic road between IZNIK and SALERNO
11:25 - 11:45 Simac Anita: When Geometry Becomes Art: Bridging Art and Geometry in the Classroom
11:45 - 12:00 Hustiuc Nicoletta: Stem activities in eTwinning projects
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12:10 - 12:30 Holanda Leandro: Designing Culturally Sustaining Learning Environments: The Role of AI, STEAM, and Project-Based Learning
12:30 - 12:50 Videnovik Maja: From Challenge to Opportunity: How AI and Gamification Enhance Motivation and Engagement in the Classroom
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Section 9: STEAM in Action – How Arts Enrich STEM Learning and Well-Being (Chair Istileulova Yelena)

11:00 - 11:05 Istileulova Yelena: How Arts Enrich STEM Learning and Well-Being
11:05 - 11:30 Makrides Gregoris: The STEAME-Academy Evolution: Latest Results
11:30 - 11:45 Kos Miha: From STEM to THE MAJESTIC: Covering Illustrations, Sonnets and Diabetes
11:45 -12:00 Jeran Marko: Poetry from the Laboratory: Red Cabbage as a Sustainable pH Indicator and Poetry as a Teaching Tool
12:00 - 12:15 Cizelj Boris: Silver Economy
12:15 - 12:30 Adnyana Wayan Kun: Rethinking Ordinary Objects in Contemporary Painting Creation
12:30 - 12:45 Pozdorovkina Irina, Rezvukhina Lidiia, Bliznyuk Elena, Zuykova Anna:Creative Wellbeing Through Plein Air Painting: A Balance between Academic Tradition and Intuition
12:45 -13:00 Istileulova Yelena: STEAM in Action: From Atomic Structure to Well Being through Music and Digital Interpretation of Lucretius
13:00 Plenary lecture: Papanikos Gregory: From TES (Technē, Epistēmē, Sophia) to STEAM: Bridging Ancient and Modern Conceptions of Knowledge

Editorial

With the participation of world top scientists from the fields and integration of science in international artistic production, Socratic lectures strive to present scientific and artistic excellence to the students, involve them in the creation of science and art and push forward development of curricula within university education.

14th Socratic Lectures symposium took place online on April 17, 2026.

It featured two plenary lectures, 9 scientific sessions, a poster session and the student session with about 240 active participants. With 48 submissions received, the Proceedings of the 14th Socratic Lectures is organized into four distinct sections: Part I focuses on breast cancer research, followed by medicine in Part II, physics in Part III, and interdisciplinary sciences in Part IV. Part II Medicine features contents from clinical medicine, material science and physiotherapy. Close collaboration between different fields is especially important for optimal treatment of a patient and activities of Socratic Lectures have since the initiation in 2008 focused on uniting the available knowledge for the benefit of the patients. This has always been the spirit of the Socratic Lectures activities.

Part II: The front cover features The Swimmers (2019) by the contemporary artist Marguerite de Saint Champs. With its fluid, serene turquoise washes and raw, sketched anatomical silhouettes suspended in a horizontal state of motion, the artwork maps human kinetics as a pure trajectory of balance and physical extension. For this volume dedicated to Medicine, Biocompatible Materials, and Physiotherapy, the image serves as a visual metaphor. It encapsulates the core pillars of physical rehabilitation and biomechanical engineering: understanding the forces governing the musculoskeletal framework, mapping the path of locomotive recovery, and celebrating the resilient elasticity, mobility, and serene vital grace of the human body in motion.

We conclude with a big thanks to all the participants who in the spirit of Socrates donated their contributions and to all those who made the events possible. Kindly invited to the next Socratic lectures.

Veronika Kralj-Iglič, Anna Romolo and Yelena Istileulova

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TEXTS

Review

Research Prospectives of Biomaterials in Robotic Surgery

Amon Mojca[1], Petrič Miha[2,*]

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Abstract:

Biomaterials are essential to the advancement of robotic surgery, enhancing surgical precision, facilitating tissue healing, and reducing complications. These materials support the integration of robotic systems with human tissues, improving the efficacy and safety of surgical interventions. Ongoing developments in biomaterials, especially the integration of smart, nanostructured, and biodegradable materials, are poised to greatly improve surgical outcomes and extend the applications of robotic surgery. However, overcoming challenges such as ensuring biocompatibility, managing material degradation, and addressing regulatory concerns is essential for their widespread clinical implementation.

Future research in biomaterials for robotic surgery holds significant promise to enhance surgical precision, improve patient safety, and optimize clinical outcomes. As technological progress continues, the integration of smart, customizable, and biocompatible materials into robotic systems will not only enhance surgeons' capabilities but also minimize complications and accelerate patient recovery with reduced long-term health. In this work we present the recent advancements in the field of robotic surgery.

Keywords Robot assisted surgery; Implants; Biocompatibility; Endocrine disrupting chemicals; Surgical precision; Patient safety.

1. Robotic surgical interventions

Robotic surgery allows surgeons to perform complex procedures with greater precision, flexibility, and control, than traditional methods. Robotic-assisted surgery devices include several components, including a console that allows surgeons to view a 3D reconstructed model of the surgical field and control the movement of surgical instruments (Picard et al., 2019). Such a bedside system includes mechanical arms that hold and manipulate surgical tools as needed by the surgeon, along with additional carts that store and support the necessary hardware and software components. During robotic-assisted surgery, the surgeon sits close to the patient. A small camera and surgical instruments are inserted through small incisions, allowing the surgeon to visualize the surgical field on a video monitor and manually manipulate the robotic arms that mimic the surgeon's actions. These multi-arm robotic systems feature advanced visual feedback and controlled movements. Robotic surgery could offer several advantages over conventional open surgery, including reduced pain, blood loss, risk of infection, less scarring, shorter hospital stays and shorter recovery times (Marescaux & Diana, 2015; Wen et al., 2014).

Robotic surgery is increasingly being adopted due to its enhanced visual capabilities, improved dexterity, and better ergonomic support for surgeons (Khajeh et al., 2023; Hopkins et al., 2020; Markar et al., 2011; Safiejko et al., 2022; Kamarajah et al., 2020). These robotic platforms facilitate implant placement with sub-millimeter accuracy, thereby minimizing the risk of nerve damage and implant malposition. The precision of robotic navigation is also contingent on the visibility of biomaterials in intraoperative scans, including fluoroscopy and 3D CT imaging. In recent studies, researchers reviewed over 247 publications on robotic technical skill metrics, spanning manual rating scales, simulators, and AI-driven performance tools. Although many AI models demonstrated accuracy rates of ≥90% in controlled laboratory settings, validation in real surgical environments showed accuracy levels ranging from 67% to 100% (Boal et al., 2024). AI systems frequently utilize sensor-integrated simulators and smart surgical instruments to capture force application, motion trajectories, and procedural errors, enabling objective assessment of surgical performance and skill acquisition. Moreover, robotic guidance significantly improves pedicle screw placement accuracy, with clinically acceptable Grade A/B placement rates frequently approaching 98–99%, while also reducing intraoperative revision rates, radiation exposure, and perioperative blood loss compared with conventional manual or fluoroscopy-guided techniques (Wei et al., 2022).

Biomaterials play an essential role in the design and integration of these implants and guidance interfaces, supporting both surgical precision and patient safety. A scoping review of 129 studies published up to mid-2022 revealed that most AI interventions remained at low levels of autonomy, predominantly offering the assistance rather than task autonomy; these interventions were largely focused on non-clinical models, such as in silico simulations or animal studies (Vasey et al., 2023). Biomaterial sensors, such as those providing force and tactile feedback, are essential components of these systems, facilitating real-time data capture and enhancing their overall functionality (Miyazaki et al., 2019).

Surgical robots are regulated as medical devices by the FDA and European CE marking, but a clear framework for evaluating these systems, particularly their AI components, is lacking. The IDEAL framework (Idea, Development, Evaluation, Assessment, and Long-term follow-up), which aims to improve the evaluation of complex interventions, is being adapted for robotic surgery. It includes stages from first-in-human evaluation to long-term follow-up, with newer adaptations providing guidance on preclinical evaluations of surgical devices (Marcus et al., 2024). Currently, most intraoperative AI applications in robotic surgery are in the preclinical phase, characterized by low autonomy and diverse evaluation methods. As AI systems gain higher autonomy, the focus will shift from AI-specific metrics to process outcomes. Future research should emphasize standardized evaluation and structured reporting to ensure the safe integration of used technologies.

2 The role of biomaterials and robotic surgery

2.1 Physical and radiological characteristics of the biomaterials

Biomaterials are indispensable in robotic surgery, particularly as minimally invasive techniques and robotic technologies continue to evolve. Robotic surgical systems rely on biomaterials in a variety of ways, such as implants guided by robotic technology, force or pressure sensors, surgical simulators, tactile interfaces at robotic consoles, and biomaterials that serve as trackable objects. Additionally, next-generation robotic platforms are exploring algorithms capable of automatically detecting implant edges (Gómez-de-Gabriel & Harwin, 2015; Cazalini et al., 2017). Machine learning models, trained on the unique textures and densities of materials, enhance robotic targeting. To ensure optimal system performance, the biomaterials must possess consistent radiological profiles or include contrast features that aid AI in recognizing key elements. The success of robotic surgery is heavily influenced by the physical and radiological characteristics of the biomaterials used. If a material is too radiolucent, robotic guidance systems may struggle to provide real-time feedback. Conversely, if it is too reflective, imaging artifacts or misinterpretations may occur. Furthermore, if not properly calibrated, machine learning systems may fail to accurately recognize the object. Although biomaterials are essential in abdominal surgeries, their use carries inherent risks. Current research focuses on improving biocompatibility, reducing infection rates, and preventing adhesion formation to optimize patient outcomes. Clinicians must remain aware of potential complications and incorporate the latest advancements in biomaterial technology to minimize risks (Nikam et al., 2023).

2.2 Biocompatibility of materials

Biomaterials play a pivotal role in robotic surgery, as implants must exhibit compatibility with both robotic instrumentation and the biological environment of the human body. Commonly used biomaterials include titanium and its alloys, particularly Ti-6Al-4V, and polyether ether ketone (PEEK). Titanium alloys are widely utilized because of their excellent biocompatibility, high corrosion resistance, favorable mechanical properties, and capacity to support osseointegration, making them suitable for robotic spinal procedures such as pedicle screw and rod systems. PEEK, a high-performance thermoplastic polymer, is frequently employed in spinal cages and cranial implants because its elastic modulus more closely resembles that of cortical bone, thereby reducing stress shielding and implant subsidence. Additionally, the radiolucent nature of PEEK enables improved intraoperative and postoperative imaging assessment, which is particularly advantageous in robotic and image-guided surgical procedures (Toth et al., 2006). Despite stringent regulatory requirements for biomaterial safety and performance, challenges remain regarding long-term clinical effectiveness. Potential risks include inflammatory or immune responses, material degradation, wear debris generation, and inadequate osseointegration, all of which may affect implant longevity and clinical outcomes. Therefore, rigorous preclinical testing and long-term post-market surveillance remain essential to ensure patient safety and optimize surgical performance.

2.3 Potential risks associated with biomaterials

Biomaterials, including surgical meshes, sutures, implants, and surface coatings, play a critical role in tissue repair, reinforcement, and reconstruction in abdominal surgery. Despite their substantial clinical benefits, their application may be associated with several biological and mechanical risks requiring careful consideration. Following implantation, biomaterials interact dynamically with host tissues and may trigger a foreign body response characterized by protein adsorption, macrophage activation and fusion into foreign body giant cells, chronic inflammation, and fibrous capsule formation. Persistent inflammatory responses can contribute to fibrosis, chronic pain, impaired tissue integration, and, in severe cases, implant failure or rejection (Anderson et al., 2008).

Mechanical complications may also arise due to material fatigue, stiffness mismatch, fiber fracture, shrinkage, or degradation of biomaterials such as polyethylene terephthalate (PET) and expanded polytetrafluoroethylene (ePTFE) meshes. These changes can compromise structural integrity and potentially lead to tissue erosion, adhesion formation, or inflammatory reactions. Furthermore, progressive mechanical degradation or loss of implant

integrity over time may increase the risk of hernia recurrence or injury to surrounding tissues and organs.

Synthetic biomaterials, particularly polypropylene-based meshes, are also susceptible to bacterial colonization and biofilm formation, which may complicate treatment because biofilms provide microorganisms with increased resistance to host immune responses and antimicrobial therapies. Biocompatibility-related issues can additionally impair tissue healing and excessive fibrotic remodeling may contribute to scar formation and functional impairment. In degradable biomaterials, the release of degradation byproducts, such as acidic compounds generated during hydrolysis of polymers including polylactic acid (PLA), may alter local tissue pH and induce irritation or inflammatory reactions. Although uncommon, hypersensitivity or allergic reactions to biomaterial components, additives, metals, or preservatives have also been reported.

3. Future research prospectives of biomaterials in robotic surgery

Ongoing innovation in biomaterials in robotic surgery is pivotal to advancing minimally invasive, personalized, and regenerative surgical approaches (Chatterjee et al., 2024). Furthermore, there is an increasing demand for the development of advanced biomaterials that are not only biocompatible but also exhibit smart, responsive characteristics, ensuring both their functionality and safety over the long term without adverse health effects.

3.1 Potential association of biomaterials and endocrine system

The potential long-term effects of biomaterials, particularly from synthetic polymers such as PVC and polyurethane, on the endocrine system are of significant concern. These materials can release plasticizers, such as phthalates and bisphenol A (BPA), which are known endocrine disruptors. Chronic exposure to these chemicals can alter hormonal balance, affect fertility, and increase the risk of cancer. However, more long-term human data are required to fully understand these risks. Recent studies have underscored that bisphenol A, phthalates, and other plasticizers can interfere with endocrine function, impacting reproductive and metabolic health. These substances may leach from implanted polymers, further complicating their safety profile. Additionally, plastic-related chemicals, including phthalates and bisphenols, have been identified as endocrine-disrupting chemicals (EDCs), neurotoxicants, and potential carcinogens. Such chemicals are linked to various health hazards, including metabolic disorders and cardiovascular diseases, as highlighted in recent reviews (Eales et al., 2022).

3.2 *Biomaterials for enhanced tissue regeneration*

The integration of mesenchymal stem cells (MSCs) with biomaterials in abdominal surgery represents a promising strategy for enhancing tissue regeneration and wound healing. MSCs exert therapeutic effects primarily through paracrine signaling by releasing bioactive factors that promote cell proliferation, angiogenesis, extracellular matrix remodeling, and immunomodulation, including macrophage polarization toward anti-inflammatory phenotypes (Wei et al., 2013). However, the clinical application of stem cell-based therapies remains limited by challenges related to cell sourcing, viability, tumorigenic potential, and regulatory issues. Increasing evidence suggests that many MSC effects are mediated by extracellular vesicles and exosomes, which offer advantages such as lower immunogenicity, improved safety, and easier handling. MSC-derived exosomes carry proteins, growth factors, and microRNAs involved in tissue repair and represent a promising cell-free approach for improving biomaterial integration and regenerative outcomes (Tan et al., 2024).

3. Conclusions

The integration of biomaterials in abdominal robotic surgery holds substantial promise for enhancing surgical outcomes; however, several challenges remain, including issues related to biocompatibility, mechanical properties, infection risks, and regulatory hurdles. Advancements in smart biomaterials, 3D printing, and nanotechnology, coupled with the establishment of standardized evaluation protocols, are essential for addressing these challenges and maximizing the potential of robotic surgery.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Host Metabolic Status and Biomaterial–Tissue Interactions in NMIBC Surgery

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Abstract:

Body composition and metabolic health are increasingly recognised as important determinants of surgical and oncological outcomes. In uro-oncology, conditions such as sarcopenia, myosteatosis, obesity, and malnutrition have been associated with increased perioperative complications, impaired recovery, reduced treatment tolerance, and poorer prognosis. In non-muscle-invasive bladder cancer (NMIBC), however, these host-related factors remain insufficiently integrated into current clinical risk stratification models, which are predominantly focused on tumour characteristics.

The review summarises current evidence regarding the role of body composition and metabolic status in NMIBC surgery and perioperative management. Particular emphasis is placed on computed tomography (CT)-based body composition analysis, including skeletal muscle index (SMI) and skeletal muscle density (SMD), together with nutritional and metabolic assessments such as body mass index (BMI), bioimpedance analysis (BIA), Nutritional Risk Screening 2002 (NRS-2002), and serum albumin. Alterations in skeletal muscle and adipose tissue are increasingly linked to systemic inflammation, immune dysregulation, metabolic dysfunction, and impaired tissue recovery.

Evidence from surgical oncology, particularly radical cystectomy cohorts, consistently demonstrates associations between sarcopenia, myosteatosis, postoperative morbidity, prolonged hospitalisation, and reduced survival. Emerging studies further suggest that metabolic and nutritional parameters may influence recurrence and progression in NMIBC treated with transurethral resection of bladder tumour (TURBT), although available data remain limited. Overall, body composition represents a clinically relevant but underutilised component of NMIBC management. Integrating CT-derived muscle metrics and nutritional assessment into perioperative evaluation may improve risk stratification, support personalised surgical decision-making, and optimise TURBT and surveillance strategies.

Keywords: NMIBC; Body composition; Sarcopenia; Myosteatosis; TURBT; Metabolic Status; Surgical outcomes; CT imaging; SMI; Personalised surgery

1. Body Composition and Metabolic Dysfunction in Uro-Oncology

1.1. Current clinical challenges in Uro-Oncology

Non-muscle-invasive bladder cancer (NMIBC) represents approximately 75% of newly diagnosed bladder cancers and remains a major clinical and economic challenge worldwide. Although survival outcomes are generally favourable, NMIBC is associated with high recurrence rates and a risk of progression to muscle-invasive disease, requiring long-term surveillance with repeated cystoscopy, urinary cytology and imaging. This intensive follow-up places a substantial burden on patients and healthcare systems and contributes to the high lifetime cost of bladder cancer care (Lenis et al., 2020; Sung et al 2021; Chou et al., 2015). Current treatment decisions and prognostic assessment in NMIBC are primarily based on tumour-related features, including stage, grade, tumour size, multiplicity and the presence of carcinoma in situ. Established risk models, such as those developed by the European Association of Urology (EAU) and and the European Organisation for Research and Treatment of Cancer (EORTC), provide valuable prognostic guidance; however, they remain largely centred on tumour biology. As a result, host-related systemic and metabolic factors that may influence recurrence, cancer progression (**Figure 1**), treatment tolerance and surgical outcomes are still insufficiently integrated into routine risk stratification (Mossanen & Gore, 2014; Isharwal & Konety, 2015).

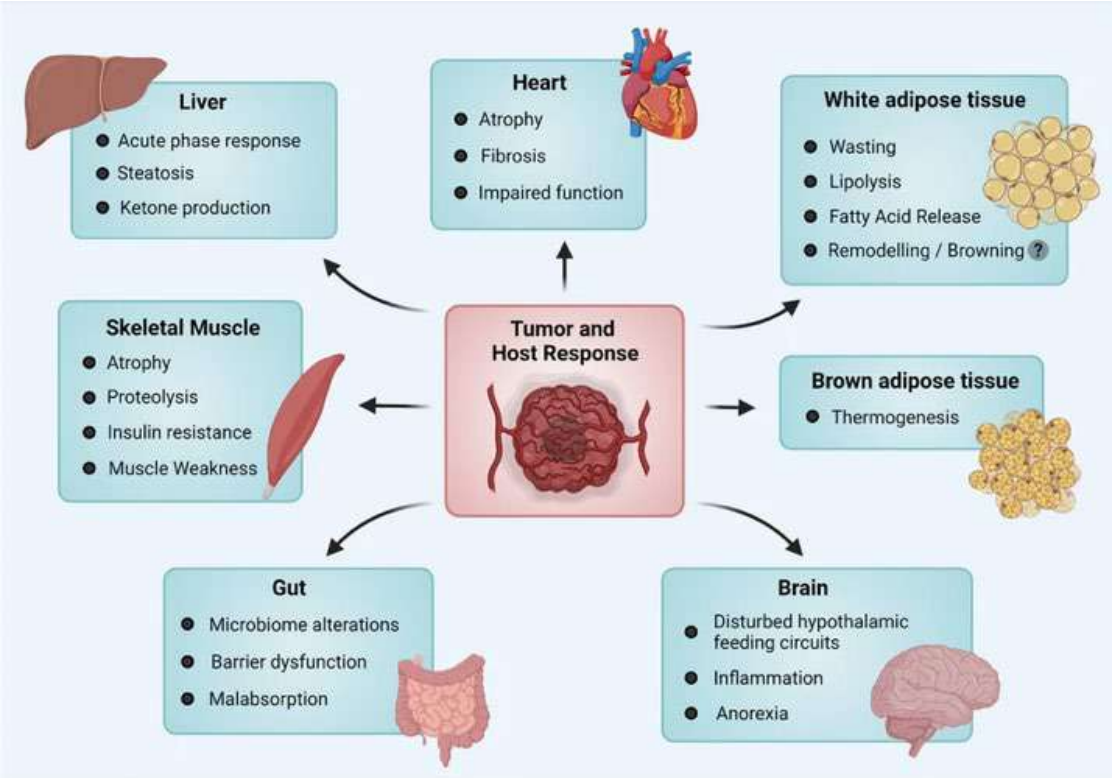

Figure 1. Tumour–Host Metabolic Crosstalk Driving Cancer Progression

2. Assessment of Skeletal Muscle and Adipose Tissue

2.1 The objective evaluation of muscle mass, muscle quality, and fat distribution

Although body composition is increasingly recognised as an important factor in oncology, its prognostic role in non-muscle-invasive bladder cancer (NMIBC) remains insufficiently defined. Most evidence linking sarcopenia and myosteatosis with poorer survival, increased postoperative complications, and adverse oncological outcomes originates from muscle-invasive bladder cancer and radical cystectomy cohorts rather than NMIBC populations. Nevertheless, computed tomography, CT- based body composition analysis has emerged as a valuable and objective approach for evaluating skeletal muscle quantity and quality using routinely acquired imaging, supporting its growing potential in uro-oncological risk stratification (Babjuk et al., 2022; Alameddine et al., 2018).

2.2 Translational Research Challenges and Future Directions

In NMIBC, accumulating evidence suggests that nutritional and metabolic status may provide clinically relevant prognostic information beyond conventional tumour characteristics. Nutritional and inflammation-related indices, including the Controlling Nutritional Status score (CONUT) score, Geriatric Nutritional Risk Index (GNRI), and Prognostic Nutritional Index (PNI), have been associated with recurrence and progression risk, indicating that systemic metabolic and nutritional factors may influence tumour behaviour and treatment response. However, currently used prognostic systems, including the European Organisation for Research and Treatment of Cancer, and European Association of Urology risk models, remain predominantly based on clinicopathological tumour variables and demonstrate only moderate predictive performance, particularly in contemporary Bacillus Calmette–Guérin (BCG)-treated cohorts. These limitations underscore the need for additional biomarkers capable of better capturing biological heterogeneity, systemic metabolic status, and tumour–host interactions in NMIBC progression. In this context, CT-derived body composition biomarkers, including skeletal muscle index, skeletal muscle density, visceral adiposity, and myosteatosis, may represent promising complementary tools for more personalised prognostic assessment and future precision surgical management strategies (Sun et al., 2025; Claps et al., 2023).

3. Surgical Outcomes in Bladder Cancer

3.1. Sarcopenia and Cancer

Sarcopenia, characterised by progressive loss of skeletal muscle mass and function, has been consistently associated with increased postoperative complications, poorer treatment response, prolonged recovery, and adverse oncological outcomes across multiple malignancies. In cancer patients, sarcopenia reflects reduced physiological reserve together with systemic inflammation, metabolic dysregulation, and cancer-related catabolism (Mayr et al., 2018; Fukushima & Koga, 2022).

In bladder cancer, most evidence originates from muscle-invasive disease and radical cystectomy cohorts, where reduced skeletal muscle mass has been linked to higher perioperative morbidity and poorer survival outcomes. CT-based body composition analysis enables objective assessment of skeletal muscle quantity and quality, including skeletal muscle index (SMI) and skeletal muscle density (SMD), and has emerged as a promising tool for personalised risk stratification in uro-oncology (Elhakim et al., 2023).

Although evidence in non-muscle-invasive bladder cancer (NMIBC) remains limited, growing data suggest that sarcopenia and related metabolic alterations may also influence recurrence, progression, treatment tolerance, and long-term clinical outcomes.

3.2. Myosteatosis and Cancer

Myosteatosis, characterised by fatty infiltration of skeletal muscle and impaired muscle quality, has emerged as an important prognostic factor in oncology. Computed tomography (CT) enables objective assessment of skeletal muscle index (SMI) and skeletal muscle density (SMD) from routine imaging, allowing evaluation of both muscle quantity and quality.

Nutritional and metabolic status may additionally influence tumour biology, immune response, treatment tolerance, and clinical outcomes. Commonly used assessments include body mass index (BMI), waist circumference, bioelectrical impedance analysis (BIA), Nutritional Risk Screening 2002 (NRS-2002), and serum albumin levels (Mayr et al., 2018).

4. Metabolic and Nutritional Biomarkers in NMIBC Risk Stratification

4.1. Systemic Metabolic Alterations in Oncology

Increasing attention has recently been directed toward the role of body composition and metabolic status in cancer progression and clinical outcomes. Host-related factors such as sarcopenia, myosteatosis, obesity, and malnutrition are increasingly recognised as important systemic determinants that may influence tumour biology, immune response, treatment tolerance, postoperative recovery, and long-term survival. These alterations reflect complex interactions between metabolism, inflammation, nutritional status, and cancer-related physiological stress.

4.2. Integrating Metabolic Biomarkers into NMIBC Care

In non-muscle-invasive bladder cancer (NMIBC), emerging evidence suggests that metabolic and nutritional biomarkers may provide additional prognostic information beyond conventional tumour-based risk factors. Integration of CT-derived body composition parameters and nutritional assessments may therefore improve personalised risk stratification and support more individualised therapeutic and surveillance strategies.

5. Future Uro- Surgery Perspectives

5.1. Towards Personalised NMIBC Management

The advances in non-muscle-invasive bladder cancer (NMIBC) management are expected to increasingly incorporate host-related biological and metabolic factors alongside conventional tumour characteristics. Growing evidence suggests that body composition, nutritional status, systemic inflammation, and metabolic dysfunction may influence perioperative recovery, treatment response, recurrence, and disease progression. Integrating these parameters into existing prognostic frameworks may therefore improve risk stratification and support more personalised clinical decision-making. CT-based body composition analysis represents a particularly promising approach because it enables objective and reproducible assessment of skeletal muscle quantity and quality using routinely acquired imaging. Combined with nutritional, functional, and laboratory biomarkers, these assessments may help identify vulnerable patients at increased risk for postoperative complications or adverse oncological outcomes. Such strategies could support personalised perioperative optimisation, including nutritional intervention, prehabilitation, physical rehabilitation, and tailored surveillance protocols.

5.2. Clinical Translational Perspectives in NMIBC Risk Stratification

Further prospective multicentre studies are needed to validate body composition biomarkers in NMIBC populations and determine their integration into contemporary prognostic models including the risk classifications. A better understanding of tumour–host interactions, metabolic dysfunction, and nutritional status may ultimately support the transition from predominantly tumour-centred management toward a more personalised and biologically integrated approach to NMIBC surgery and surveillance.

6. Conclusions

The advances in regenerative medicine and biomaterials may further contribute to personalised uro-oncological care. The development of biologically active biomaterials, tissue-engineered biomaterials, and regenerative strategies capable of improving tissue healing, reducing inflammation, and supporting functional recovery may represent an important complementary direction in bladder cancer surgery and reconstruction. Together, integration of metabolic, imaging, and biomaterial-based approaches may contribute to the development of next-generation personalised surgical management in NMIBC.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Cardiovascular and Metabolic Health: Endocrine Disrupting Chemicals and Biomaterials

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Abstract:

Endocrine and metabolic dysfunctions may be related to environmental endocrine disrupting chemicals (EDCs), which can alter hormone-related organs and are thus associated with different health problems. Medical biomaterials, devices and all implants must be biocompatible to reduce the risk of adverse effects. Biocompatibility has applications in a variety of biomedical fields, including orthopedic implants and devices, dental implants and materials, and cardiovascular devices. Although most medical biomaterials are rigorously tested for biocompatibility and safety, including toxicity and endocrine disruption, the risk may derive from known or suspected endocrine disruptors; the material is implanted or used for long time; or the material may break down or degrade into smaller, active compounds during the aging process.

The article presents the insight into common environmental chemicals and theoretical concerns about the potential consequences of the long-term presence of artificial materials in the body. Future research directions in the field of biocompatibility should include developing a better understanding of the interactions between biomaterials, their molecular mechanisms and the endocrine system. Clinical experimental studies are needed to examine endocrine associations and ensure that the industry requires identification of products containing potentially harmful materials.

Keywords: Cardiovascular health; Metabolic syndrome; Endocrine disrupting chemicals; Obesity; Obesogens; Implants

1. Environmental pollutants and health

1.1. Environmental chemicals

There is growing interest in the possible health threat posed by endocrine disruptors as different chemicals which are substances in our environment, food, and consumer products and interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. There is substantial evidence that endocrine disruptors have effects on reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism, and cardiovascular endocrinology during aging (Diamanti-Kandarakiset et al., 2009; Moroni et al., 2020; Fan et al., 2023; Huang et al., 2024; Liang et al., 2025).

1.2. Toxicology of endocrine disruptors

Cardiometabolic disorders and aging-related diseases are a growing public health problem. Among the known cardiometabolic risk factors are compounds that may induce endocrine and metabolic dysfunctions, such as endocrine disrupting chemicals (EDCs). Those EDCs can alter hormone-related organs and thus be linked to a wide range of non-communicable cardiometabolic diseases. EDCs are chemicals which contribute to health problems by interfering with the physiological production and target effects of hormones with proven impact on a number of endocrine systems. EDCs are natural or synthetic compounds present in the environment which can interfere with hormone synthesis and normal physiological functions. Most EDCs tend to bind to steroid hormone receptors including the oestrogen receptor, progesterone receptor and androgen receptor and disrupt the actions of endogenous hormones; they may also induce abnormal physiological functions of different systems (Lee et al., 2013). Over the past 20 years, scientific knowledge about endocrine disruptors has increased exponentially, particularly about bisphenols such as BisPhenols A (BPA), and it is now accepted that low doses of BPA can alter the function of hormone-related organs and thus be linked to a wide range of non-communicable cardiometabolic diseases (Chen et al., 2025).

1.3. EDCs and obesity

The etiology of the obesity epidemic has been partly attributed to high caloric uptake, a lack of physical activity and sedentary lifestyle. However, beside a genetic predisposition and lifestyle modifications, scientific research implies the impact of environmental substances in the generative roots of obesity, explained as "obesogens" – molecules which inappropriately regulate lipid metabolism and adipogenesis to promote obesity (Grün & Blumberg 2006; Tabb & Blumberg, 2006; Jaskulak et al., 2025).

The excessive weight is one of the top ten health risks in the world and the number of overweight people in the world is now greater than the number of undernourished. The prevalence of obesity defined as body fat greater than 25% in men or greater than 30% in women, has risen dramatically in wealthy, developed countries, and it is also on the rise in poor nations. The rise in the incidence of obesity matches the rise in the use and distribution of different chemicals that may be playing a role in generation of obesity (Baillie-Hamilton 2002; Diamanti-Kandarakis et al., 2009; Jaskulak et al., 2025), suggesting that EDCs may be linked to this epidemic. Obesity has deleterious effects on human health by increasing the risk of associated metabolic abnormalities such as insulin resistance, hyperinsulinemia, hypertension, and dyslipidemia—all components of the metabolic syndrome—which constitute, in turn, major risk factors for the development of diabetes mellitus type 2 and coronary heart disease.

The obesity phenotype may lead to a dysmetabolic state with atherogenic, inflammatory, prothrombotic abnormalities which not only accelerate the progression of cardiovascular diseases but also create favorable "subsoil" for an acute myocardial infarct (Poirier & Després, 2003; Assenza et al., 2025). Therefore, the cardiovascular system is also a target of environmental chemicals which interfere with intracellular signaling of hormonal and inflammatory pathways. A link between exposure to EDCs and the occurrence of cardiovascular diseases, myocardial infarction, hypertension, and altered cardiac electrophysiology was demonstrated (Fu et al., 2020).

1.4. Research problem of EDCs

The specific health impacts of EDCs remain debated, and their tissue and molecular targets are poorly understood. Shu et al. (2019) identified the association of bisphenols (BPA) molecular signatures with cardiometabolic phenotypes in mice and humans. Their multi-tissue, multi-omics investigation provides strong evidence that EDCs perturb diverse molecular networks in central and peripheral tissues and it offers insights into the molecular targets which potentially link different EDCs to various human health disorders (**Figure 1**).

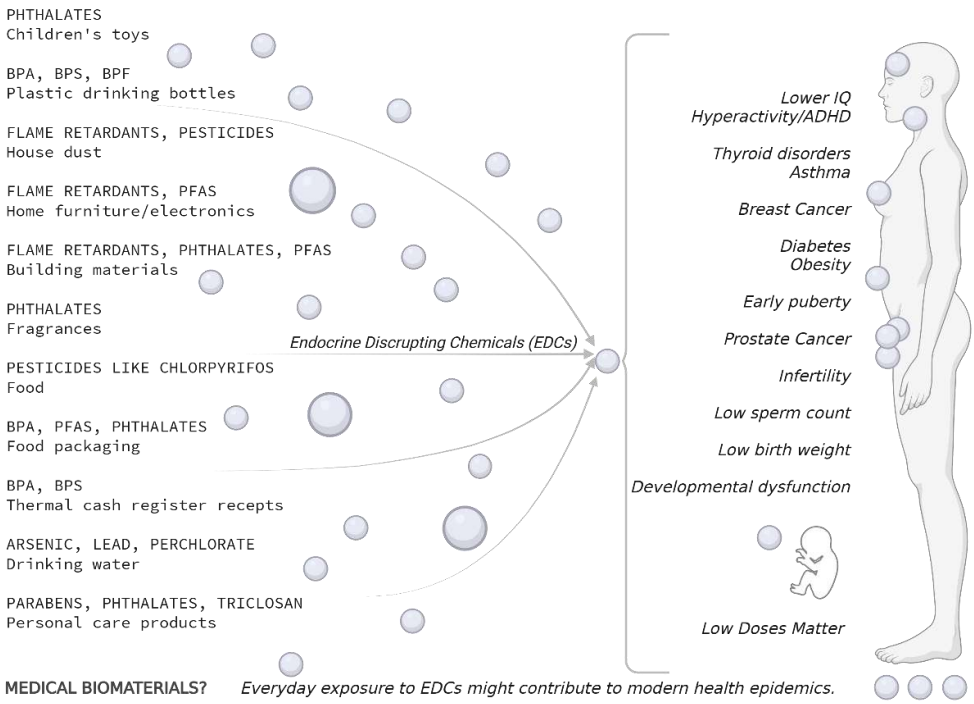

Figure 1. Association between different EDCs and potential health disorders.

The mechanism of EDCs influences the molecular level and cardiometabolic risks is not yet to be fully elucidated, especially considering the complexity contributed by species-, chemical-, and dose-specific effects. Moreover, different experimental and analytical methodologies employed by different studies pose challenges when comparing findings across studies.

To explore the molecular mechanisms of EDCs in a systematic manner, Zamora et al. (2024) established a data-driven computational approach to meta-analyze 30 human, mouse, and rat liver transcriptomic datasets for 4 EDCs, BPA, bis(2-ethylhexyl) phthalate (DEHP), tributyltin (TBT), and perfluorooctanoic acid (PFOA). They found that the rat, mouse, and human BPA studies showed highly variable transcriptomic patterns, providing molecular support for the variability in BPA responses. It is important that their bioinformatics workflow will be used in a new toxicogenomic database to study a broad range of environmental toxicants and tissues to better understand their influence on complex human diseases (Zamora et al., 2024). Although EDCs represent a significant public health concern, there are no other standard methods to determine the effect of EDCs on human beings.

To summarize, EDCs represent a broad class of molecules from different environmental industrial chemicals, plastics and plasticizers, fuels, and other chemicals present in widespread use and might be even present in different medical implants, drug delivery systems, or coatings. Biomedical materials are normally biocompatible; however, in long-term contact with body tissues they might potentially cause endocrine issues if implanted or used chronically or if degraded into harmful compounds.

To conclude, the recommendations for a better understanding of the effects of endocrine disruptors are not negligible, including promoting basic and clinical research of different implanted biomaterials and their epigenetic potential in transmitted pathways, which can

be modeled in laboratory *in vitro* and *in vivo* models. Therefore, more basic and clinical research is needed to understand the effects of EDCs, invoke the precautionary principles, and advocate involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness.

3. Conclusions

More experimental studies are needed for better insights into differences of molecular mechanisms of various EDCs to elucidate the underlying connections between chemical exposure and disease risks. Furthermore, the long-term impact of various biocompatible biomaterials implanted in the human body may not be a negligible part of the research from an endocrine perspective.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Air Pollution and Vascular Biomaterial Remodeling

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Abstract:
Air pollution is increasingly recognised as an independent cardiovascular risk factor. Fine particulate matter and ultrafine particles can transport toxic elements and metalloids, promoting systemic inflammation, oxidative stress, endothelial dysfunction, and vascular injury. Toxic elements such as cadmium, lead, mercury, arsenic, nickel, and chromium may contribute to vascular damage, while essential trace elements, including selenium, zinc, copper, manganese, and molybdenum, support redox balance and cellular homeostasis. However, the role of toxic–essential element imbalance in cardiovascular disease remains insufficiently understood.
Recent translational studies combine environmental exposure assessment, human biomonitoring, and vascular phenotyping. Exposure is typically evaluated using environmental data together with biomarkers measured in blood and urine. Cardiovascular status can be assessed through non-invasive vascular measurements and, where clinically indicated, analysis of vascular tissue obtained during surgery. Advanced analytical methods enable quantification of toxic and essential elements and evaluation of their associations with vascular alterations.
Chronic exposure to air pollution–related toxic elements is expected to be associated with endothelial dysfunction, inflammation, and early vascular remodeling. Imbalances between toxic and essential elements may correlate with the severity of vascular injury. Combining biomonitoring with tissue-level analysis may therefore provide new mechanistic insights and support the identification of early biomarkers of environmentally driven vascular damage.
Overall, integrating environmental exposure assessment, biomonitoring, and vascular tissue analysis offers a promising framework for understanding environmentally related cardiovascular disease. Considering both toxic and essential elements may improve cardiovascular risk assessment, early detection, and the development of targeted preventive strategies.

Keywords: Air pollution; Cardiovascular disease; Toxic elements; Essential elements; Trace elements; Endothelial dysfunction; Vascular pathology; Biomonitoring; Environmental health

1. Environmental Exposure and Cardiovascular Risk

Air pollution is increasingly recognized as an important independent cardiovascular risk factor. Exposure to airborne particulate matter and environmental toxicants may promote systemic inflammation, oxidative stress, endothelial dysfunction, and early vascular injury. Particulate matter (PM) comprises microscopic solid particles and liquid droplets generated from traffic emissions, industrial activities, combustion processes, and environmental dust. According to aerodynamic diameter, PM is categorized into coarse particles ($PM_{10} \leq 10$ μm), fine particles ($PM_{2.5} \leq 2.5$ μm), and ultrafine particles (< 0.1 μm). Due to their small size, fine and ultrafine particles can penetrate deeply into the respiratory tract and enter the circulation, where they contribute to vascular and cardiovascular damage.

Airborne particles frequently carry toxic metals and metalloids, including cadmium, lead, mercury, arsenic, nickel, and chromium. Chronic exposure to these elements may result in tissue accumulation and cellular dysfunction, thereby enhancing vascular injury and cardiometabolic risk. In contrast, essential trace elements such as selenium, zinc, copper, manganese, and molybdenum are involved in antioxidant defence, redox regulation, and cellular homeostasis. Evaluating the interaction between toxic and essential elements may therefore improve understanding of environmentally driven cardiovascular disease and support earlier risk detection and prevention.

2. Biomonitoring of Toxic and Essential Elements

Environmental exposure assessment and biomonitoring are increasingly used to investigate the cardiovascular effects of air pollution and toxic elements. Epidemiological evidence suggests that ambient and household air pollution contribute substantially to global cardiovascular morbidity and mortality, accounting for millions of premature deaths annually (Liang et al., 2020; Münzel et al., 2021). These environmental exposures are now considered relevant alongside established cardiovascular risk factors such as hypertension, diabetes, dyslipidaemia, obesity, and smoking.

Fine particulate matter and ultrafine particles represent particularly harmful components of polluted air because they contain complex mixtures of organic compounds, reactive gases, and metal-associated contaminants. Following inhalation, these particles may directly translocate into the bloodstream or trigger pulmonary inflammatory and oxidative responses that subsequently affect the vascular system. Such mechanisms have been associated with endothelial dysfunction, vascular inflammation, autonomic imbalance, arterial stiffness, thrombosis, and accelerated atherosclerosis (Finch & Conklin, 2016; Liang et al, 2020).

Biomonitoring approaches based on blood, urine, and tissue analysis enable quantitative assessment of cumulative exposure to toxic and essential elements. Combined with vascular phenotyping and environmental exposure data, these methods may provide valuable mechanistic insight into environmentally related cardiovascular injury and facilitate the identification of early biomarkers of vascular dysfunction.

3. Vascular Remodeling and Endothelial Dysfunction

Endothelial dysfunction is increasingly considered one of the earliest and most important pathophysiological mechanisms linking environmental exposure to cardiovascular disease. The vascular endothelium plays a central role in maintaining vascular homeostasis through regulation of vasodilation, inflammation, thrombosis, oxidative balance, and vascular remodelling. Under physiological conditions, endothelial cells preserve nitric oxide (NO) bioavailability, inhibit inflammatory activation, and prevent platelet aggregation and leukocyte adhesion. However, exposure to air pollutants and toxic metals may disrupt endothelial homeostasis through excessive reactive oxygen species (ROS) production, impaired endothelial nitric oxide synthase (eNOS) activity, and activation of pro-inflammatory signalling pathways. Reduced NO bioavailability together with increased oxidative stress contributes to impaired vasodilation, vascular stiffness, inflammation, and progressive vascular injury (Liang et al., 2020; Finch & Conklin, 2016; Münzel et al., 2018; Bayo, 2023).

4. Translational Approaches to Environmentally Driven Cardiovascular Disease

Experimental and clinical studies have demonstrated that exposure to $PM_{2.5}$ is associated with increased arterial stiffness, elevated blood pressure, impaired endothelial-dependent

vasodilation, progression of carotid intima–media thickness, and enhanced atherosclerotic plaque formation. Air pollution has also been linked to elevated circulating inflammatory mediators, endothelial adhesion molecules, and oxidative stress biomarkers, which promote monocyte recruitment, macrophage activation, lipid accumulation, and vascular remodelling, thereby contributing to the initiation and progression of atherosclerosis (Liang et al., 2020; Finch & Conklin, 2016).

Toxic elements represent an additional and increasingly recognized environmental cardiovascular risk factor. Unlike essential trace elements required for normal physiological processes, non-essential metals such as cadmium, mercury, arsenic, and lead have no known biological role and may exert harmful effects even at low concentrations. Chronic exposure may lead to tissue accumulation and disruption of antioxidant defence systems, mitochondrial function, lipid metabolism, and endothelial signalling pathways. These mechanisms have been associated with hypertension, coronary artery disease, stroke, heart failure, and accelerated vascular ageing, while recent systematic reviews and meta-analyses further support the relationship between toxic element exposure and cardiovascular risk (Nucera et al., 2024; Cheema et al., 2025).

In contrast, essential trace elements including selenium, zinc, copper, manganese, and molybdenum contribute to antioxidant defence, cellular metabolism, and redox homeostasis. Disturbances in the balance between toxic and essential elements may therefore influence vascular integrity and susceptibility to cardiovascular injury. Despite increasing evidence linking environmental exposures with cardiovascular disease, the complex interactions between toxic and protective trace elements remain insufficiently understood.

5. Conclusions

Current evidence highlights the need for integrated translational approaches that combine environmental exposure assessment, biomonitoring, vascular phenotyping, and direct tissue-level analysis. Such strategies may improve understanding of the mechanisms underlying environmentally driven vascular injury and support the identification of early biomarkers of endothelial dysfunction and vascular remodeling. Ultimately, a deeper understanding of environmental cardiovascular risk factors may contribute to earlier detection, improved risk stratification, and the development of targeted preventive and therapeutic strategies for environmentally exposed populations.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Biomaterials for Vascular Reconstruction: Present Challenges and Future Perspectives

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Abstract:

Decellularized vascular scaffolds represent a promising strategy in vascular tissue engineering because they aim to remove cellular and nuclear material while preserving the extracellular matrix (ECM) architecture, biochemical composition, and mechanical properties of native vessels. However, decellularization is inherently a balance between effective cell removal and preservation of matrix integrity, since physical, chemical, and enzymatic treatments can alter ECM ultrastructure, surface composition, and biological activity (Gilbert et al., 2006; Crapo et al., 2011). Although decellularized vascular matrices provide a biologically active scaffold that can support cell adhesion, remodeling, and tissue integration, their clinical performance remains limited by thrombosis, insufficient endothelialization, intimal hyperplasia, and long-term patency challenges (Moroni & Mirabella, 2014; Li Y. et al., 2023). This review summarizes traditional methods for vascular scaffold decellularization and discusses current evaluation criteria, including residual DNA removal, ECM preservation, mechanical competence, hemocompatibility, and endothelialization potential. Particular attention is given to emerging approaches such as non-thermal irreversible electroporation (NTIRE), which may assist cellular disruption while reducing chemical damage, and cold plasma functionalization, which may improve scaffold surface wettability, bioactivity, and cell–matrix interactions (Phillips et al., 2010; Lombardo et al., 2024). Finally, the review considers the future potential of combining electroporation-assisted decellularization with plasma-based surface functionalization to improve vascular scaffold preparation, luminal endothelialization, and blood-contacting performance.

Keywords: Vascular scaffolds; Decellularization; Extracellular matrix; Electroporation; Plasma functionalization; Endothelialization; Tissue engineering

1. Introduction

Cardiovascular tissue engineering aims to develop vascular substitutes that can restore blood flow while preserving mechanical stability, hemocompatibility, and biological integration. Although autologous vessels remain the preferred option for many bypass procedures, they are not always available in sufficient quality or length. Synthetic vascular grafts are clinically useful in large-diameter vessels, but their performance remains limited in small-diameter applications, where thrombosis, restenosis, poor endothelial recovery, and compliance mismatch contribute to graft failure (Moroni and Mirabella, 2014; Ren et al., 2015; Li Y. et al., 2023).

Decellularized vascular scaffolds have therefore gained attention as biological alternatives to synthetic conduits. Decellularization aims to remove cellular and nuclear material, which may contain immunogenic donor antigens, while preserving the extracellular matrix (ECM), the three-dimensional network of proteins and polysaccharides that provides structural support and biochemical signals to cells. Unlike inert materials, the ECM can influence cell adhesion, migration, proliferation, differentiation, and tissue remodeling, making it an active biological microenvironment rather than a passive support structure (Gilbert et al., 2006; Crapo et al., 2011). In vascular scaffolds, this retained matrix is particularly valuable because it can preserve vessel-like architecture and provide cues for host cell repopulation, endothelialization, and integration (Moroni and Mirabella, 2014; Li J. et al., 2023).

However, decellularization alone is not sufficient to ensure graft function. Small-diameter vascular scaffolds are directly exposed to circulating blood, and the absence of a continuous endothelial lining can expose thrombogenic ECM components, allowing platelet adhesion, clot formation, reduced perfusion, and tissue damage. For this reason, re-endothelialization of the luminal surface is a central requirement for long-term patency and functional vascular regeneration (Mazloomnejad et al., 2023). At the same time, conventional decellularization protocols based on detergents, enzymes, osmotic treatments, and physical disruption may damage ECM ultrastructure, alter surface properties, or reduce biological cues needed for later cell attachment (Gilbert et al., 2006; Crapo et al., 2011).

These limitations have encouraged interest in emerging and complementary strategies. Non-thermal irreversible electroporation (NTIRE), an electrical method that disrupts cell membranes while aiming to limit thermal and chemical damage, has been investigated as a potential physical adjunct for vascular decellularization (Phillips et al., 2010). In parallel, cold plasma functionalization has been explored as a post-decellularization surface treatment capable of modifying wettability and surface chemistry to improve cell–material interactions, although vascular-specific validation remains limited (Lombardo et al., 2024). This review therefore examines traditional vascular scaffold decellularization, scaffold evaluation criteria, electroporation-assisted approaches, plasma functionalization, and the future potential of combining these strategies to improve vascular scaffold performance.

2. Traditional Methods for Vascular Scaffold Decellularization

Traditional vascular scaffold decellularization usually combines physical, chemical, and enzymatic approaches because no single method can reliably remove cellular material while fully preserving extracellular matrix (ECM) structure. Physical methods, such as freeze–thawing, agitation, pressure, and sonication, can disrupt cell membranes and improve reagent penetration, but they are rarely sufficient as stand-alone techniques. Therefore, they are commonly combined with detergents, enzymes, chelating agents, nucleases, and extensive washing steps to remove cellular debris and residual reagents (Gilbert et al., 2006; Crapo et al., 2011).

Chemical methods remain central to most vascular decellularization protocols. Detergents are particularly important because they solubilize cell membranes and help remove cytoplasmic and nuclear components. However, their effectiveness must be balanced against possible damage to ECM proteins and bioactive molecules. Ionic detergents such as sodium dodecyl sulfate (SDS) and sodium deoxycholate are effective for removing cells and nucleic acids, but they can disrupt collagen organization, reduce glycosaminoglycans (GAGs), and alter vascular microstructure. In contrast, non-ionic detergents such as Triton X-100 are generally milder and may better preserve protein-rich ECM structures, although they may be less effective for complete decellularization when used alone (Gilbert et al.,

2006; Li J. et al., 2023; Mazloomnejad et al., 2023). Zwitterionic detergents such as CHAPS, or 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate, have also been used because they may preserve collagen, elastin, and GAGs better than stronger ionic detergents, although their effects remain protocol-dependent (Li J. et al., 2023).

Enzymatic treatments can further assist decellularization. Trypsin may help detach cells from the ECM and improve the penetration of later reagents, while deoxyribonuclease and ribonuclease, commonly abbreviated as DNase and RNase, degrade residual nucleic acids. Nevertheless, enzymatic exposure must be carefully controlled, since prolonged digestion can damage laminin, fibronectin, elastin, collagen networks, and other matrix components required for endothelial cell attachment and vascular function (Gilbert et al., 2006; Moroni and Mirabella, 2014).

For vascular tissues, perfusion-based decellularization is particularly relevant because the native vascular lumen can be used to deliver reagents more uniformly through the scaffold. Compared with simple immersion or diffusion-based methods, perfusion can improve detergent distribution, cellular debris removal, and preservation of vessel architecture and patency (Crapo et al., 2011; Mazloomnejad et al., 2023). Overall, traditional vascular decellularization should be understood as a tissue-specific optimization process. The selected protocol must remove cellular and nuclear material while preserving ECM architecture, mechanical behavior, and the surface features needed for later endothelialization and hemocompatibility (Li Y. et al., 2023; Moroni & Mirabella, 2014).

3. Evaluation of Decellularized Vascular Scaffolds

The evaluation of decellularized vascular scaffolds should confirm not only the removal of cellular material, but also the preservation of the extracellular matrix (ECM) features required for vascular function. Commonly used criteria for effective decellularization include residual double-stranded DNA (dsDNA) below 50 ng/mg dry ECM, DNA fragments shorter than 200 base pairs, and absence of visible nuclear material after hematoxylin and eosin (H&E) or 4′,6-diamidino-2-phenylindole (DAPI) staining (Crapo et al., 2011). However, DNA removal alone does not fully define scaffold quality. Residual cellular proteins, xenogeneic antigens such as α-Gal, N-glycolylneuraminic acid (Neu5Gc), SDa antigen, and major histocompatibility complex (MHC) molecules may also influence host responses and should be considered when evaluating biological compatibility (Li Y. et al., 2023).

Because vascular scaffolds must withstand blood pressure and surgical manipulation, ECM preservation and mechanical competence are equally important. Collagen and elastin integrity should be assessed because collagen contributes to tensile strength, while elastin supports vessel recoil and compliance. Other ECM molecules, including laminin, fibronectin, glycosaminoglycans (GAGs), and basement membrane collagen IV, are also relevant because they support endothelial cell adhesion, migration, and re-endothelialization (Gilbert et al., 2006; Moroni & Mirabella, 2014; Mazloomnejad et al., 2023). Therefore, vascular scaffold evaluation should include mechanical tests such as burst pressure, compliance, tensile strength, and suture retention strength, together with histological and biochemical analysis of ECM structure.

Functional testing is especially important for vascular applications. Even a scaffold that meets decellularization criteria may fail if it promotes thrombosis or does not support endothelial coverage. Evaluation should therefore include platelet adhesion, clotting behavior, hemolysis, endothelial cell attachment, proliferation, spreading, and the ability to form a confluent endothelial layer on the luminal surface (Ren et al., 2015; Li J. et al., 2023). For modified scaffolds, additional tests are required. For example, plasma-functionalized decellularized ECM materials should be assessed for surface chemistry, wettability, cell adhesion, hemocompatibility, and mechanical preservation, while electroporation-treated arteries should be evaluated for cellular loss together with collagen, elastin, and luminal endothelial recovery (Phillips et al., 2010; Lombardo et al., 2024). Overall, scaffold evaluation must integrate structural, biochemical, mechanical, immunological, and blood-contacting criteria to determine whether the final vascular matrix is suitable for regeneration.

4. Future Perspectives of Decellularized Vascular Scaffolds

Future vascular scaffold preparation will likely require multi-step protocols that address cell removal, extracellular matrix (ECM) preservation, and luminal surface optimization as connected but distinct objectives. Traditional decellularization methods can effectively remove cellular and nuclear material, but chemical, enzymatic, and physical treatments may also disrupt ECM architecture, reduce glycosaminoglycans (GAGs), alter adhesive proteins, and affect the mechanical or biological properties of the scaffold. Therefore, future protocols should be tissue-specific and should use the mildest effective strategy capable of achieving adequate decellularization while preserving collagen, elastin, basement membrane structure, and matrix cues required for endothelialization and remodeling (Gilbert et al., 2006; Crapo et al., 2011).

Within this framework, non-thermal irreversible electroporation (NTIRE) may serve as a physical cell-disruption step. NTIRE uses short electrical pulses to destabilize cell membranes and induce irreversible membrane defects, leading to cell death without directly digesting the ECM. Experimental arterial studies have shown that NTIRE can produce markedly decellularized arterial segments while preserving detectable collagen and elastin structures, suggesting potential value for vascular scaffolds where matrix integrity is essential (Phillips et al., 2010). However, NTIRE should currently be considered an experimental adjunct rather than a complete replacement for conventional decellularization. Its effectiveness depends on pulse parameters, electrode geometry, treatment volume, thermal control, and the removal of cellular debris after membrane disruption. For this reason, future protocols may combine electroporation with perfusion, washing, or mild chemical pretreatment to improve debris removal while limiting ECM damage (Crapo et al., 2011; Koo et al., 2022).

Cold plasma functionalization may complement this approach by addressing the post-decellularization surface. After cellular removal, vascular scaffolds may retain native-like matrix architecture but still present a luminal surface that is not optimal for blood contact or endothelial cell attachment. Plasma treatment can modify surface wettability, introduce reactive chemical groups, and improve cell–material interactions without necessarily altering bulk scaffold mechanics. Lombardo et al. (2024) showed that nitrogen/hydrogen (N_2/H_2) cold plasma treatment of decellularized ECM films increased nitrogen- and oxygen-containing functional groups, improved hydrophilicity, enhanced early cell adhesion and proliferation, and maintained tensile properties, although the study was performed on bovine pericardium dECM films rather than tubular vascular grafts (Lombardo et al., 2024). In vascular applications, plasma-based surface modification may be particularly relevant because surface chemistry influences protein adsorption, platelet adhesion, endothelial cell behavior, and hemocompatibility (Ren et al., 2015; Li Y. et al., 2023).

Electroporation and plasma functionalization should therefore be viewed as potentially complementary rather than competing strategies. Electroporation could assist cellular disruption while reducing reliance on harsh detergents, whereas plasma functionalization could tune the preserved luminal ECM surface to improve wettability, endothelial attachment, and blood compatibility. Such a sequential approach remains hypothetical and requires direct vascular-specific validation. Future studies should evaluate whether electroporation-assisted decellularization followed by plasma functionalization improves residual DNA removal, ECM preservation, mechanical behavior, platelet interaction, endothelial cell coverage, and long-term graft patency. If successful, this integrated strategy could shift vascular scaffold preparation from simple cell removal toward a more functional approach combining gentle decellularization, surface bioactivation, and regenerative vascular remodeling (Moroni & Mirabella, 2014; Mazloomnejad et al., 2023).

5. Conclusions

Decellularized vascular scaffolds should be viewed not simply as acellular tubes, but as biologically active matrices whose function depends on preserved extracellular matrix **(ECM)** structure, reduced immunogenicity, mechanical competence, hemocompatibility, and restoration of a functional endothelial lining. Traditional decellularization protocols can effectively remove cellular and nuclear material, but they must be optimized for each tissue because physical, chemical, and enzymatic treatments may also alter collagen, elastin, glycosaminoglycans **(GAGs)**, adhesive proteins, and growth factors that are

essential for scaffold bioactivity and vascular mechanics (Gilbert et al., 2006; Crapo et al., 2011; Moroni & Mirabella, 2014).

The major challenge for decellularized vascular matrices remains the translation from a structurally preserved scaffold to a functional blood-contacting graft. In particular, small-diameter vascular grafts continue to face limitations related to thrombosis, intimal hyperplasia, calcification, incomplete endothelialization, and long-term patency (Li Y. et al., 2023; Li J. et al., 2023). Therefore, future scaffold development should integrate objective decellularization criteria with functional evaluation of mechanical properties, platelet interaction, endothelial cell attachment, and in vivo performance.

Emerging strategies such as non-thermal irreversible electroporation **(NTIRE)** and cold plasma functionalization may contribute to this next generation of vascular scaffolds. NTIRE may assist cellular disruption while limiting damage to key ECM components, whereas plasma treatment may tune the luminal surface to improve wettability, cell–matrix interactions, and hemocompatibility (Phillips et al., 2010; Lombardo et al., 2024). However, both approaches require further vascular-specific validation. Overall, the future of decellularized vascular scaffolds will likely depend on integrated, multi-step protocols that combine gentle decellularization, preserved matrix mechanics, surface functionalization, and rapid re-endothelialization to create a stable, non-thrombogenic, and regenerative vascular interface (Ren et al., 2015; Mazloomnejad et al., 2023).

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Review

Is running good for bone health?

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Abstract:
Running is a widely practiced and accessible form of physical activity with well-established health benefits; however, its effects on bone health remain unclear. This narrative review examines key mechanical, systemic, and individual factors influencing bone adaptation in runners. Current evidence suggests that running may provide some skeletal benefit compared with inactivity, particularly at directly loaded sites such as the lower limb. However, bone responds most effectively to dynamic, high-magnitude, high-rate, and multidirectional loading, whereas the repetitive and high-volume nature of distance running may provide a less potent osteogenic stimulus. Mechanosensory saturation may further limit the effectiveness of prolonged repetitive loading. Beyond mechanical factors, bone health in runners is influenced by systemic factors such as energy availability, hormonal status and sleep, as well as individual factors including training history, early sport specialization, and prior bone stress injuries. Collectively, these findings suggest that running alone may not be sufficient to optimize bone health. Incorporating varied, higher-impact loading alongside running, while addressing systemic and individual determinants, may provide a more effective strategy for maintaining and improving skeletal health. In this review. The aim of this narrative review is to examine some key factors that influence bone adaptation in runners and to discuss their role in long-term bone health.

Keywords: Distance running; Bone health; Bone mineral density; Osteogenic loading; Low energy availability; Bone stress injury

1. Introduction

Running is one of the most popular and accessible forms of physical activity worldwide (Scheerder et al., 2015) and has become increasingly popular over the last 50 years (Vitti et al., 2020). Considering physical inactivity is one of the most significant global health burdens (Katzmarzyk et al., 2022) running is one of the most important forms of physical activity for maintaining and improving health (Hespanhol Junior et al., 2015). Running is also embraced for a variety of reasons including competition, recreation, and social engagement (Shipway & Holloway, 2016). Due to its broad health benefits running is therefore recommended and should be promoted publicly to support policies that support running programs and its benefits (Hespanhol Junior et al., 2015).

Despite the health benefits, running is not free from adverse events. Running-related musculoskeletal injuries are very common among novice and experienced runners (Kakouris et al., 2021). Runners have a 2.5-fold higher injury incidence than individuals in other sports, which shows that running is a "risky" sport, especially considering overuse injuries (Kemler et al., 2018). Some running related overuse injuries are also bone stress injuries (BSI). Although not common in the general population, BSI may account for up to 20 % of all injuries in athletes and military recruits who participate in activities such as marching, running, jumping and dancing (Bennell et al., 1996; Kelly et al., 2024; Milgrom et al., 1985; Rizzone et al., 2017). BSI are a result of repetitive mechanical loading and exist along a pathology continuum beginning with stress reaction and can progress to stress fracture or complete fracture (Warden et al., 2014). Given the relatively high incidence of bone stress injuries in runners, bone health (commonly measured via BMD; Nattiv et al., 2007; Shuhart et al., 2019) emerges as one of key factors influencing both injury risk and adaptation to mechanical loading (Warden et al., 2021a).

Although the mechanical role of bone is to resist external forces, repetitive loading, which is below the complete fracture threshold, results in microdamage formation (Hoenig et al., 2022; Warden et al., 2014). Microdamage is a normal and necessary phenomenon occurring in all skeletons independent from athletic ability (Warden et al., 2021a). Microdamage enables energy dissipation and is a stimulus for targeted remodelling, which involves activation of remodelling units, consisting of an advancing front of bone-resorbing osteoclasts followed by rows of bone-forming osteoblasts (Burr, 2002; Warden et al., 2014). These mechanisms highlight that bone adaptation to repetitive loading is not inherently beneficial but rather depends on the balance between damage accumulation and repair processes (Warden et al., 2021a). While bone stress injuries represent the extreme end of maladaptation, more subtle alterations in bone structure and density may also occur without clinical symptoms. Although, running is likely more beneficial for bone health than doing nothing, the osteogenic potential of running remains unclear, as its effects on bone health likely depend on a complex interaction of mechanical, systemic, and individual factors.

Therefore, the aim of this narrative review is to examine some key factors that influence bone adaptation in runners and to discuss their role in long-term bone health.

2. Methods

This review is based on a descriptive overview of existing scientific literature previously identified and collected in the field of bone tissue adaptation and bone health in runners. Original and review articles were included and further supplemented through screening of reference lists of relevant publications. The aim of this review was not to provide a comprehensive or reproducible search strategy, but rather to present and interpret current evidence relevant to bone tissue adaptation in runners and associations with bone health. The search was limited to articles published in English and in peer-reviewed journals. The identified studies were subsequently organized into thematic sections based on their content. Artificial intelligence-assisted image generation (ChatGPT, OpenAI) was used to create conceptual figure based on author-written manuscript content.

3. Bone adaptations and running: mechanisms and modifying factors

The phenomenon that mechanical loads can affect bone architecture in living beings was first described by Wolff's Law (Frost, 2004). Bone formation, remodelling and damage accumulation processes are stimulated by mechanical strain. More precisely, bone cells are responsive to local mechanical strain expressed in their precise vicinity by routine stresses supplied by activities of daily living. Therefore, the determinants of bone adaptation in response to mechanical loading involve all aspects of the strain environment, including strain magnitude, strain rate, strain frequency, strain distribution, number of loading cycles and rest-recovery periods. All of these components are interlinked and interdependent and together contribute to possible osteogenic effect and potency of mechanical loading (Hart et al., 2017), however some derivatives of strain magnitude are not as relevant to the topic and are outside of scope of this review.

3.1. Mechanical loading characteristics and bone adaptation

Magnitude of strain is key for bone adaptative responses (Hart et al., 2017). Based on "mechanostat theory" different magnitudes of strain continuum elicit bone resorptive, regenerative or formative responses (Frost, 2004). Bone adapts to magnitudes that are above its minimum effective strain thresholds (Ehrlich & Lanyon, 2002; Frost, 2004). It is important to note that based on current understanding, muscle exerts contractile forces onto the skeleton to effectuate movement, providing bone with its largest voluntary delivery of stimulus; superseding gravitational load, e.g. ground reaction forces (DiGirolamo et al., 2013; Hart et al., 2017; Ireland et al., 2014). Furthermore, if indeed maximal strains govern bone adaptations and internal muscle forces are the dominant effectors of bone strain, then maximal muscle force should determine the osteogenic potential of an exercise modality (Ireland et al., 2014). This association of high peak force with bone adaptation is also demonstrated in running athletes of different disciplines (e.g. race walking, long and middle distance running and sprinting) where tibial bone strength is positively associated with the speed of the event and hence the magnitude of ground and presumably internal muscular forces (Ikedo et al., 2016; Wilks et al., 2009).

Strain rate refers to the speed at which strain is applied. Strain rate has been shown to be a critical driver of osteogenesis independent of strain magnitude (Hart et al., 2017). Rapidly applied dynamic loads are more effective in stimulating bone formation compared to slowly applied loads, highlighting the importance of high-rate loading in osteogenic exercise (Hart et al., 2017). In addition, strain location direction and gradient also influence the osteogenic stimulus, with irregular and unusual distribution (spatial delivery) of strain further enhancing bone formation (Gross et al., 1997; Robling et al., 2006). Thus mechanosensitive machinery in bone responds best to high-magnitude loads introduced at high rates (Warden et al., 2021b).

Bone adaptation to loading is site specific (Tenforde & Fredericson, 2011; Warden et al., 2021b) and also exhibits directionality, with bone mass being added and structural geometry developing in accordance with the direction of applied load (Warden et al., 2020). Thus, weight-bearing activities incorporating impulsive loading, particularly those involving some degree of intermittent, explosive jumping and/or sprinting with rapid changes of direction, have the greatest osteogenic potential (Wardenmet al., 2021a). This does not mean that distance running is without skeletal benefit. Cross-sectional evidence suggests that distance runners often demonstrate equal or slightly greater BMD than inactive controls, particularly at directly loaded sites such as the leg or calcaneus (Garofolini & Taylor, 2019), although benefits are less consistent at the lumbar spine or total body (Herbert et al., 2021; Scofield & Hecht, 2012). A review by Scofield and Hecht similarly concluded that running is generally associated with equivalent or slightly higher BMD than inactive controls, but lower BMD than higher-impact sports (Scofield & Hecht, 2012). Therefore, running may be better than inactivity for bone health, but its osteogenic effects appear site-specific and suboptimal compared with more varied loading.

Furthermore, findings presented above are in line with a review by Tenforde & Fredericson (2011) who evaluated differences in bone health caused by sports participation. Athletes who participated in high-impact and multidirectional loading sports, including soccer and basketball, consistently had greater bone mineral density (BMD) and enhanced bone geometric properties compared with those who participated in distance running. In a cross-sectional study of males, soccer players had greater BMD at all sites including the

lumbar spine, femur, calcaneus compared with distance runners and sedentary controls (Fredericson et al., 2007). Additionally, Milgrom et al. (2000) performed in vivo tibia bone strain measurements during simulated activities unique to different sports (basketball and running) and found 50%-100% greater compression and shear strains and greater strain rates during rebound jumping compared with running. These results suggest that greater bone loading forces in basketball may stimulate bone remodelling and result in stiffer more fracture-resistant bones (Tenforde et al., 2015). Also running primarily occurs in a sagittal plane, whereas ball sports incorporate greater multidirectional movements and therefore may result in a more generalized strengthening of bone (Tenforde et al., 2015).
Collectively, these findings indicate that bone adapts most effectively to dynamic, high-magnitude, high-rate, and multidirectional loading, suggesting that repetitive, uniform activities such as distance running may be suboptimal for bone health.

3.2. Loading volume and mechanosensitivity

Strain volume is often aggregately quantified into a total number of loading cycles (Hart et al., 2017). While many combinations of strain magnitude, rate and frequency can interact to provide potent osteogenic stimuli, bone adaptation does not linearly respond to strain volume (Ozcivici et al., 2010; Qin et al., 1998), since skeletal loading duration do not elicit proportional changes in bone mass formation. Rather bone responsiveness to mechanical load eventually declines, highlighting an evident suppression of mechanosensitivity also known as mechanosensory saturation (Burr, 2002; Robling & Turner, 2009). Bone cells are thus responsive to mechanical stimuli in the short term, but their sensitivity to the stimulus wanes quickly after its initiation (Robling & Turner, 2009). Specifically, ~95 % of bone mechanosensitivity is dampened after only 20 to 40 loading cycles at physiologic thresholds, with no benefit of adding beyond 100 loading cycles with equivalent strain loading (Burr et al., 2002; Umemura et al., 1997). In simpler terms, bone cells become "deaf" to repetitive loading; implication being that after running a few minutes, bone cells find the monotonous, unidirectional loading to be boring and they stop responding (Warden et al., 2021a). Nevertheless, subsequent restoration of mechanosensitivity is crucial for effectiveness of future loading. Over 90 % of mechanosensitivity is restored with 4-8 hours of rest between repeat loading bouts (Burr et al., 2002; Robling et al., 2001). These findings confirm the need for the bone stimulus to be short, dynamic, variable which is not the case in distance running. Thus, a few minutes of a bone-centric exercise (e.g. plyometrics) later in the day after a running session may generate further bone adaptation over and above that generated solely by running (Warden et al., 2021a). The addition of bone-centric exercise requires consideration of cumulative bone loads, however approach was used to improve bone health in other endurance sports, such as cycling and swimming (Vlachopoulos et al., 2018b, 2018a).
These mechanisms suggest that high-volume, repetitive loading such as running may not provide a sufficiently effective osteogenic stimulus, since bone responds more favourably to short, dynamic and variable loading, particularly when loading bouts are separated by sufficient rest periods, which helps restore mechanosensitivity.

4. Beyond mechanical loading: systemic factors affecting runner's bone health

Mechanical loading alone does not determine bone adaptation; the skeletal response also depends on whether the athlete has sufficient systemic capacity to support bone formation and remodelling. Poor bone health is common among distance runners. For instance, up to 40 % of female adolescent cross-country runners have a dual-energy X-ray absorptiometry (DEXA) z-score of below -1 for total body or spine areal BMD (Barrack et al., 2008). There are numerous possible reasons for the inferior bone health in cross-country athletes (Hoenig et al., 2022). The most obvious is the high prevalence of low energy availability (LEA) and subsequent relative energy deficiency in sport (REDs), which replaced female athlete triad as a more comprehensive, broader term for the overall syndrome (Mountjoy et al., 2014). Up to 50 % of female runners meet the criteria for disordered eating and/or report menstrual dysfunction (Barrack et al., 2008; Dambacher et al., 2025; Rauh et al., 2020; Skorseth et al., 2020), all of which are detrimental to bone health (Mountjoy et al., 2023).

However, gymnast exhibit higher bone mass than runners despite both populations having a similar prevalence of menstrual dysfunction (Robinson et al., 1995), which might imply that running is just not a good bone-building activity (Warden et al., 2021a).

Although running itself is not the direct cause of LEA it is linked to possible societal norms, perceptions of a need for leanness, sport specific body type, dissatisfaction with body image etc. which could predispose runners to disordered eating behaviours and consequently to LEA (de Borja et al., 2021; Mancine et al., 2020). Even though a lot of the publications study female athletes, detrimental effects of REDs are similar in male athletes, although magnitude of the effects on some physiological parameters and the threshold at which these effects manifest appear to be variable between genders (Mountjoy et al., 2023). Recently, international Delphi consensus listed risk factors for development of BSI (Hoenig et al., 2025) of which a lot of those that reached consensus agreement could be associated with athlete's diet and nutritional demands. When encountering athletes with proximal or central trabecular high-risk BSIs (femoral neck, sacrum, lumbar spine), which are linked to underlying poor bone health (i.e. lower BMD; Ackerman et al., 2015; Tenforde et al., 2018), clinicians should raise suspicion about athletes bone health and possible impact of systemic factors e.g. LEA and hormonal dysfunction (Tenforde et al., 2018, 2024). This just goes to show sufficient energy intake is crucial to maintain and improve runners bone health, whether in a context of pathology or health continuum.

Another important factor when considering runner's bone and systemic health is sleep (Swanson et al., 2018). Disruption or lack of sleep impairs bone formation in otherwise healthy men (Swanson et al., 2017). Also, higher proportion of women with a history of high-risk BSI reported averaging less than 7 hours of sleep a night during the week compared with those with no previous BSI (Tenforde et al., 2024). This is consistent with military data, which showed that a combination of reduced military marching and increase in sleep duration, from 3-4 hours to a minimum of 6 hours, reduced BSI rate in military training by 62 % along with 0.5 % gain in bone mass (Finestone & Milgrom, 2008). These findings suggest that adequate sleep is essential in promoting overall skeletal adaptation.

Collectively, recognizing that bone health is not solely influenced by mechanical load parameters, but also by systemic factors such as energy availability, hormonal function, and sleep, is essential for guiding strategies and promote healthy running culture and associated behaviours to maintain and improve bone health in this high energy expenditure sport.

5. Individual factors and lifespan loading history

In addition to systemic factors, bone health in runners is also shaped by individual loading history across the lifespan. A history of playing multidirectional sport in female runners is associated with better bone health (Warden et al., 2022). This is supported by findings in military recruits who played ball sports for at least two years prior to basic military training and reported 46 % - 84 % reduction in stress fractures compared to recruits who did not play ball sports (Milgrom et al., 2000). It is also important to consider history of bone loading during growth, since it provides once in a lifetime opportunity to optimize bone size (Warden et al., 2021a). Loading in youth encourages additional bone to be added periosteally to further increase bone size (Bass et al., 2002) which exponentially increases bone strength and fatigue resistance for the amount of material added (Warden et al., 2005). This just underpins the importance of higher magnitude, high-rate, multidirectional loading in younger athletes. In contrast, early sport specialization, specifically early distance running specializers had five times the odds (OR = 5.42) of having low BMD (z score < –1.0) compared to low sport specializers (Rauh et al., 2020). Authors elaborate that results may be explained by a complex relationship of multiple interactions of sport exposure with associated behaviours and menstrual dysfunction contributing to low BMD, since they also found high prevalence of LEA and menstrual dysfunction. There is lack of running specific data on early sport specialization in relation to bone health. However, some studies show that early running specializers are at increased risk of overuse injuries (Bell et al., 2018; Pasulka et al., 2017), thus current recommendations are that single sport specialization

should be delayed until at least 14 years of age (Sugimoto et al., 2024), so to develop a robust skeleton that can withstand multidirectional loading (Warden et al., 2021a). In addition to youth and developmental factors, bone health considerations are also relevant in master runners, i.e. runners 35 years and older, who present a specific population and thus require nuanced consideration regarding runner's bone health. Nevertheless, similar to younger runners, health considerations in master runners include the goal to optimize bone health with focus on mitigating age-associated loss of bone strength and preventing BSIs (Raiser et al., 2024).

A history of injury, particularly BSI, is another important factor when considering runner's bone health. This is especially relevant for several reasons. Firstly, runners with a history of BSI are at high risk (OR = 4.99) for another BSI (Wright et al., 2015). Secondly, bone remodelling times are long, since it takes 3-6 months for volumetric BMD to return to baseline after a BSI (Popp et al., 2021). However, return to sport may happen sooner (Hoenig et al., 2023), potentially creating a mismatch between tissue recovery and perceived readiness, which is often guided by pain resolution (Popp et al., 2021). Finally, as mentioned before, BSIs are highly prevalent among runners (Rizzone et al., 2017). Collectively, these factors necessitate gradual and well-structured return to running approach that considers multifactorial nature of BSI and prioritizes the protection of long-term skeletal health (Hoenig et al., 2025).

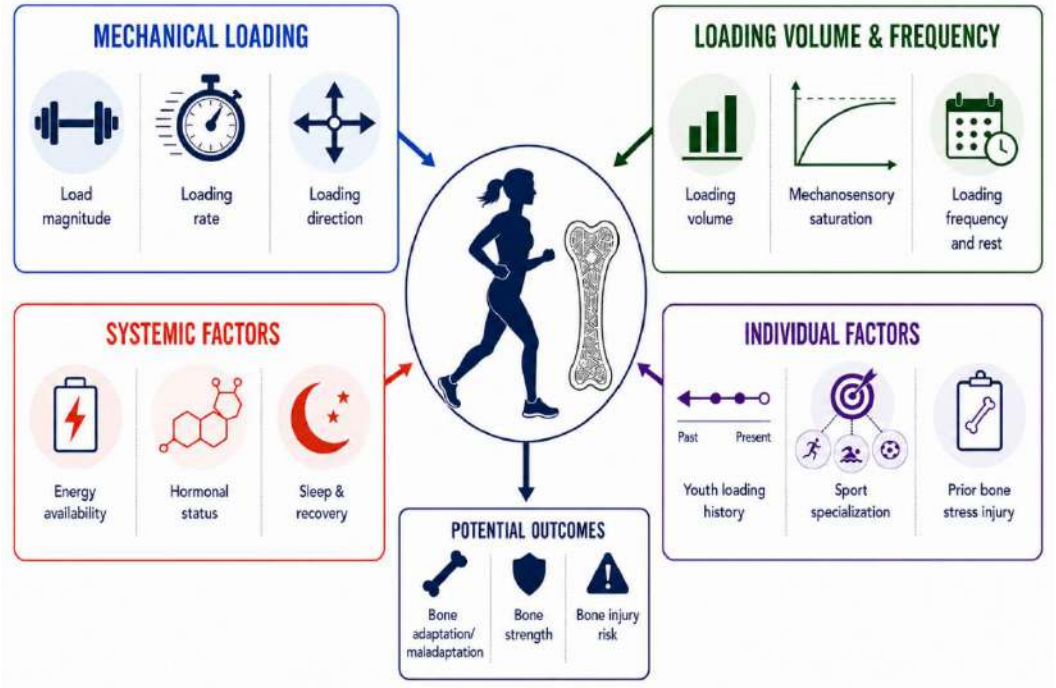

Figure 1. Factors associated with bone health in runners discussed in this review. Figure does mention exhaustive list of all possible factors that could be associated with runner's bone health. The figure was generated using ChatGPT (OpenAI) based on the content of the manuscript.

These findings highlight that bone health in runners is strongly influenced by training history across the lifespan, with early exposure to high-impact, multidirectional loading providing long-term benefits, while early specialization in distance running and prior injury may predispose to suboptimal skeletal outcomes, emphasizing the need for a lifespan and multimodal approach to optimizing bone health.

6. Limitations and future directions

Our narrative review presented arguments regarding the circumstances in which running may be beneficial or detrimental to skeletal health. We included a lot of cross-sectional and observational studies which allows for hypothesis generation but does not enable to establish causal relationships between running related factors and bone health outcomes. In addition, some findings are extrapolated from non-running populations, which may limit their applicability to runners. Finally, there is a relative lack of running-specific studies, which would capture the multiple factors in a prospective study design to really elucidate the magnitude of the effect of certain factors associated with runner's long term bone health. This highlights the need for further research in this area.

7. Conclusions

Running is a widely accessible and beneficial form of physical activity and may provide some skeletal benefit compared with inactivity, particularly at directly loaded sites such as the lower limb. However, its effectiveness as a standalone osteogenic stimulus appears limited compared to other loading variations. Bone adapts most effectively to dynamic, high-magnitude, high-rate, and multidirectional loading, whereas the repetitive and high-volume nature of distance running may provide a less potent stimulus for improving whole-skeleton bone health. In addition, bone health in runners is influenced by systemic factors such as energy availability, hormonal status and sleep, as well as individual factors including training history, early sport specialization, and prior injury. Therefore, running alone may not be sufficient to optimize bone health. Incorporating varied, higher-impact loading alongside running, while addressing systemic and individual factors, may provide a more effective strategy for maintaining and improving skeletal health.

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Research

Physiological Adaptation and Transition to Pathology: Lessons from Exercise Physiology and Ergonomics in Extreme Environments

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Abstract:
Extreme environmental conditions such as cold exposure, hypoxia, and physical load challenge human physiological homeostasis and may trigger a transition from adaptive responses to pathological processes. Understanding these mechanisms is essential not only for environmental and occupational physiology but also for clinical medicine, where similar physiological constraints occur during surgery, critical illness, and rehabilitation. This review integrates findings from three complementary research projects conducted at the Jožef Stefan Institute investigating field-based ergonomics, peripheral vascular responses to cold and hypoxia, and metabolic adaptations during prolonged normobaric hypoxic exposure. The studies demonstrate that environmental stressors interact through systemic physiological mechanisms affecting thermoregulation, microcirculation, energy metabolism, and functional performance. Cold-induced vasodilation (CIVD) emerges as a dynamic marker of physiological adaptability, while hypoxia influences both peripheral vascular regulation and whole-body metabolic balance. Together, these findings provide translational insights into vascular dysfunction, tissue perfusion, metabolic resilience, and perioperative physiology, highlighting the continuum between environmental adaptation and clinically relevant pathology.

Keywords: Cold-induced vasodilation; Hypoxia; Environmental physiology; Ergonomics; Metabolism; Thermoregulation; Surgery; Vascular function; Adaptation

1. Introduction

Human physiological systems continuously adapt to environmental challenges in order to maintain homeostasis. Exposure to cold, hypoxia, and prolonged physical activity represents a substantial stress that activates integrated cardiovascular, metabolic, thermoregulatory, and neuroendocrine responses (Mazzeo, 2008; Cheung, 2010). While these adaptive mechanisms are generally protective, excessive or prolonged exposure may lead to maladaptation and contribute to pathological processes. Understanding the factors that determine whether physiological stress results in successful adaptation or dysfunction remains a central objective of integrative physiology (Tipton et al., 2017, 2021,;Keramidas et al., 2010, 2014; Kounalakis, 2010, Mekjavic et al., 2012, 2016, 2022, 2023).

Research conducted in extreme environments offers a unique opportunity to investigate mechanisms that are highly relevant to clinical medicine. Conditions such as impaired tissue perfusion, hypothermia, metabolic stress, and reduced oxygen availability frequently occur during major surgical procedures, critical illness, and recovery following trauma (Sessler, 2016; Ince, 2005). Consequently, environmental physiology provides a useful framework for studying the continuum from physiological adaptation to pathology.

2. Field Ergonomics and Physiological Performance Under Environmental Stress

The study demonstrated that physiological strain was determined primarily by individual physical capacity rather than by absolute workload alone. Considerable inter-individual variability was observed despite identical environmental conditions and equipment loads. These findings emphasize the importance of personalized ergonomic assessment and illustrate the complex interaction between environmental demands, physical workload, and individual physiological reserve (Knapik et al., 2004; Amon, 2007).

3. Peripheral Vascular Responses to Cold and Hypoxia

The second project investigated cold-induced vasodilation (CIVD), a protective peripheral vascular response that occurs during prolonged exposure to cold. CIVD is characterized by periodic increases in blood flow and skin temperature following an initial phase of vasoconstriction. This phenomenon is believed to reduce local cold injury while preserving tissue oxygenation and viability (Lewis, 1930; Daanen, 2003; Amon, 2009).

The results revealed that normobaric hypoxia impaired peripheral temperature responses in the toes, whereas finger CIVD responses remained largely unchanged. These findings suggest regional differences in vascular adaptation and indicate that lower extremity circulation may be more susceptible to reduced oxygen availability. Importantly, aerobic training combined with altitude acclimatization improved CIVD responses, demonstrating that peripheral vascular adaptation is modifiable and influenced by physiological conditioning (Amon et al., 2012a; Felicijan et al., 2008).

Although CIVD has traditionally been investigated within the field of environmental physiology, its broader clinical significance is increasingly recognized. Variability in CIVD responses may reflect differences in vascular health, metabolic status, body composition, and physiological reserve (Daanen, 2003; Tsoutsoubi et al., 2023). Consequently, CIVD may represent a valuable integrative marker of microvascular function and individual adaptability to physiological stress.

4. Metabolic Adaptation During Prolonged Hypoxia

Comprehensive metabolic assessments included body composition analysis, meal tolerance testing, appetite regulation, hormonal responses, and measurements of resting energy expenditure. The findings demonstrated that hypoxia consistently induced a negative energy balance through a combination of increased energy expenditure and reduced energy intake. This effect was accompanied by alterations in appetite-regulating hormones and increased sympathetic nervous system activity (Mekjavic et al., 2016; Kayser, 1994; Westerterp et al., 1992).

In normal-weight participants, hypoxia prevented the increase in fat mass that occurred during normoxic exposure despite relatively modest changes in total body weight. In overweight individuals, similar reductions in appetite and increases in energy expenditure were observed. However, evidence of early insulin resistance was also detected, suggesting that metabolic responses to hypoxia may differ according to baseline metabolic status (Mekjavic et al., 2016).

5. Clinical and Translational Implications

The physiological challenges encountered in extreme environments closely parallel those observed in perioperative medicine and critical care. Surgical patients frequently experience controlled hypothermia, transient tissue hypoperfusion, metabolic stress, and altered oxygen delivery. Consequently, understanding adaptive responses to environmental stress may provide valuable insights into mechanisms underlying postoperative complications and recovery (Sessler, 2016; Ince, 2005; Carli & Scheede-Bergdahl, 2015).

Particularly relevant is the role of microvascular function in maintaining tissue viability. The ability to preserve peripheral circulation during environmental stress may reflect broader vascular resilience that influences wound healing, tissue regeneration, and recovery from surgical interventions (Ince, 2005). Similarly, the metabolic adaptations observed during hypoxic exposure provide insights into mechanisms regulating performance and energy balance, insulin sensitivity, and physiological reserve (Mekjavic et al., 2012, Mekjavic et al., 2016).

Cold-induced vasodilation emerges from these studies as a potential integrative biomarker linking vascular responsiveness, thermoregulatory capacity, and overall physiological adaptability (Amon et al., 2012b; Daanen, 2003; Tsoutsoubi et al., 2023).

Acknowledgements

This article summarizes work originating from a long-term research program in environmental physiology conducted within the research group led by at the Jožef Stefan Institute. The presented studies were performed during the bachelor's, master's, and doctoral education of at the Jožef Stefan International Postgraduate School and encompass research on cold-induced vasodilation, hypoxia, thermoregulation, metabolism, ergonomics, and human performance in extreme environments. Collectively, these investigations contributed to a broader understanding of physiological adaptation to environmental stress and its translational relevance to clinical medicine, rehabilitation, and surgical physiology.

Conflicts of Interest: The author declares no conflict of interest.

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Research

Effectiveness of Nurse-Led Peripherally Inserted Central Catheter Placement versus Physician-led PICC Insertion: A Literature Review

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Abstract:
Reliable vascular access remains essential in modern clinical practice, with peripherally inserted central catheters representing an important option for safe and effective medium- and long-term administration of intravenous therapy. In many healthcare systems, specialized Vascular Access Teams, often nurse-led, have been introduced to improve insertion efficiency, safety, and service organization delivery. A descriptive literature review was conducted using the databases Scopus, Web of Science, and PubMed to evaluate nurse-led versus physician-led peripherally inserted central catheters insertion models and the role of vascular access teams. Search terms included combinations of nurse-led, physician-led, vascular access team, intracavitary electrocardiography, tip confirmation and global development. English-language studies involving adult populations and focusing on insertion success, organizational outcomes, and included vascular access service models. A literature review identified that nurse-led vascular access team models achieve high insertion success rates, low complication rates, shorter waiting times, and improved clinical workflow efficiency. Comparative studies reported outcomes comparable to, or better than, traditional physician-led insertion models. The use of intracavitary electrocardiography improved bedside catheter tip confirmation accuracy, reduced reliance on fluoroscopy and chest radiography, shortened procedure times, and lowered healthcare costs. Evidence suggests that multidisciplinary vascular access team supported by modern technologies such as intracavitary electrocardiography represent an effective and progressive model of peripherally inserted central catheters service delivery. Procedural quality depends mainly on training, competency, experience, and adherence to standardized protocols rather than professional background alone. Further multicentre prospective studies are needed to evaluate long-term clinical and economic outcomes.

Keywords: Peripherally inserted central catheter; Nurse-led; Physician-led; Vascular access team; Vascular access device

1. Introduction

Reliable vascular access is a key part of modern health care and is required for the delivery of intravenous therapy, chemotherapy, parenteral nutrition, vasoactive medications, blood products, hemodynamic monitoring, and repeated blood sampling (Pittiruti et al., 2009, Moureau & Chopra, 2016). As healthcare systems have become more complex, the demand for safe, timely, and efficient placement of vascular access devices has increased significantly. Among available vascular access devices, the peripherally inserted central catheter (PICC) has become an important option for medium and long-term venous access due to its broad clinical applicability, relatively safe insertion method, and their role as an alternative to the centrally inserted central catheter (CICC), offering a less invasive and often safer method of placement (Patel et al., 2018).

PICC devices are widely used in oncology patients receiving chemotherapy, in patients requiring prolonged intravenous antibiotic therapy, parenteral nutrition, electrolyte replacement, and in those with difficult peripheral venous access. Compared with CICCs, PICCs represent a less invasive alternative with lower risk of certain insertion-related complications and improved bedside feasibility (Kim et al., 2025, Tsotsolis et al., 2015). Historically, PICC insertion was performed by physicians using blind techniques or fluoroscopy-guided placement, often followed by chest radiography to confirm final tip position. These traditional approaches were associated with delays in treatment initiation, increased procedural costs, radiation exposure, and workflow limitations (Pittiruti et al., 2009).

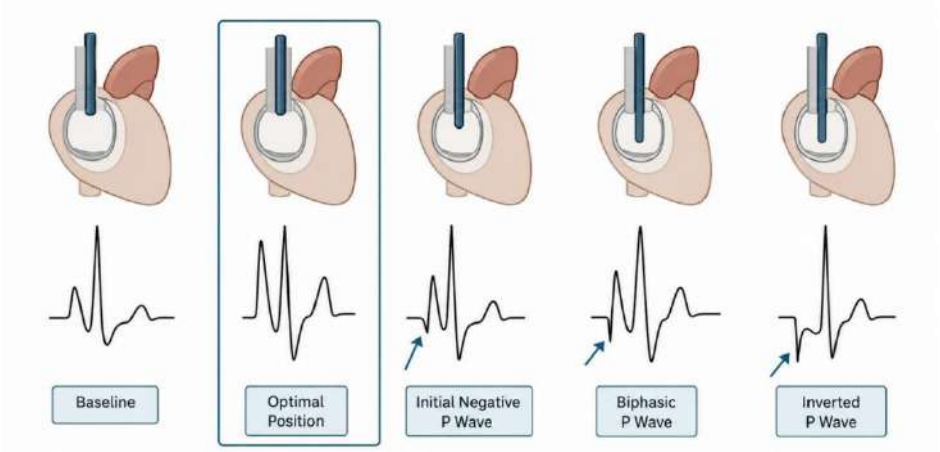

Figure 1. Schematic illustration of intracavitary electrocardiographic (IC-ECG) changes during advancement of a peripherally inserted central catheter (PICC) from the superior vena cava toward the Cavo-atrial junction and right atrium. As the catheter tip approaches the pericardial reflection, the P wave progressively increases in amplitude and becomes peaked. Maximum P-wave amplitude is observed at the Cavo-atrial junction, corresponding to the optimal PICC tip position. Further advancement of the catheter into the right atrium results in a biphasic or inverted P wave. In this study, final PICC tip placement was determined at the point of maximal P-wave amplitude, corresponding to the Cavo-atrial junction.

Over recent decades, many hospitals have introduced specialized vascular access teams (VAT), frequently led by specially trained nurses, to improve catheter insertion and vascular access management. Nurse-led PICC teams are now common in many Western healthcare systems, where they have been established to improve service availability, procedural standardization, patient flow, and quality of care (Sakai et al., 2024). However, in several countries these programs remain in earlier stages of development, and their direct institutional impact has not been fully evaluated. Traditionally, physicians were considered the primary operators for central venous access insertion. However, specialized nurse-led services have expanded in many healthcare systems and challenged this long-known model. Several studies have reported high insertion success rates and low complication rates in nurse-led PICC programs, with some institutions demonstrating reduced utilization of CICCs after implementation of dedicated nurse practitioner-led teams. In addition, the use of modern tip confirmation systems such as intracavitary electrocardiography (IC-ECG) (**Figure 1**) has further improved bedside PICC placement efficiency and accuracy (Freitas et al., 2026).

2. Material and Methods

This study was conducted as a descriptive literature review to evaluate the current evidence regarding peripherally inserted central catheter (PICC) insertion performed by nurses and physicians, as well as the contribution of specialized vascular access teams (VATs), with particular focus on the use of intracavitary electrocardiography (IC-ECK) for catheter tip confirmation and its impact on clinical, organizational, and economic outcomes.

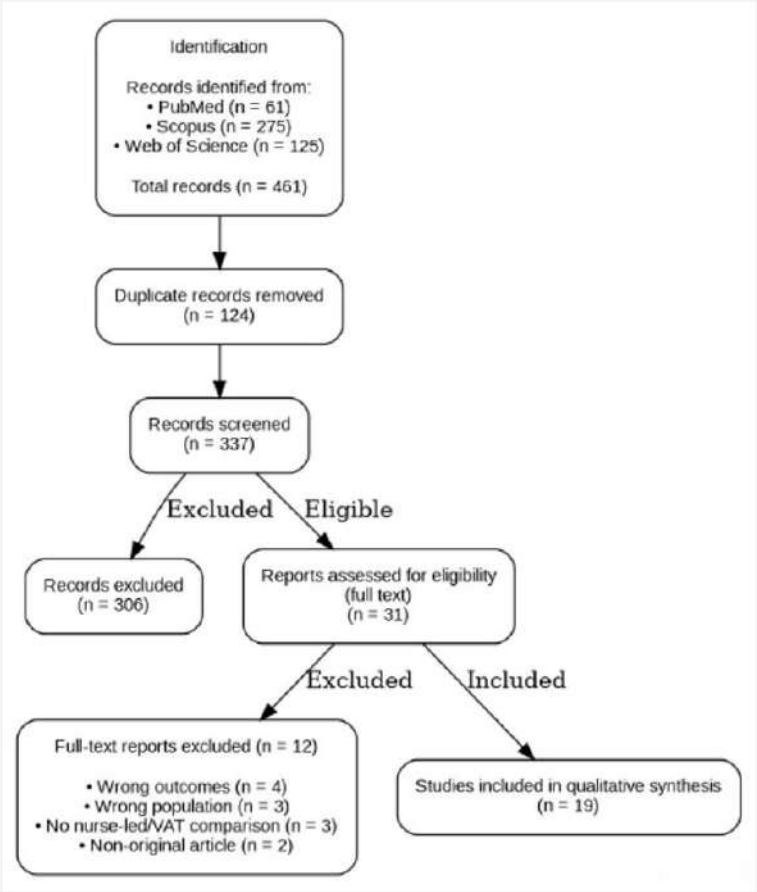

Figure 2. Prisma 2020 flow diagram illustrating the study selection process for literature review.

A literature search was performed in PubMed, Scopus and Web of Science using combination of the keywords: PICC, peripherally inserted central catheter, nurse-led, physician-led, vascular access team, IC-ECG, tip-confirmation, ultrasound-guided, and vascular access service. The search was limited to full-text articles published in English within least 10 years involving adult populations. Eligible studies evaluated nurse-led or physician-led PICC insertion, investigated the role of vascular access teams, assessed the use of intracavitary electrocardiography for catheter tip confirmation, and reported clinical, procedural, organizational, or economic outcomes related to PICC placement.

Studies involving paediatric populations, conference abstracts, editorials, letters to the editor, duplicate records, review articles, and publications not directly related to PICC insertion, vascular access teams, or IC-ECG-guided tip confirmation were excluded.

A total of 461 records were identified through database searching (PubMed, n = 61; Scopus, n = 275; Web of Science, n = 125). After duplicate removal, 337 records remained for title and abstract screening. Following the screening process, 306 records were excluded based on the predefined eligibility criteria. Thirty-one full-text articles were assessed for eligibility, of which 12 were excluded after full-text review. Consequently, 19 studies met the inclusion criteria and were included in the qualitative synthesis. The study selection process is presented in the PRISMA 2020 flow diagram (**Figure 2**).

3. Results

As the first retrospective study of its kind in Saudi Arabia reviewing four years of clinical data, the Saudi study demonstrated that a specialized nurse-led PICC service can achieve outcomes comparable with previous international reports, where ultrasound-guided PICC insertion success rates ranged from 98.6% to 100% (Alsaleh et al., 2025). The specialized nurse-led PICC team achieved a 99.1% overall placement success rate across 330 cases. Of these, 323 PICCs (97%) were successfully inserted under IC-ECG guidance within one or two attempts, while 7 PICCs (2.1%) required fluoroscopy guidance on the third attempt. Only 3 cases (0.9%) required referral to interventional radiology, where 2 PICCs (0.6%) were successfully placed, whereas 1 insertion (0.3%) was unsuccessful for both teams due to tortuous veins and small vein diameter. These findings indicate that specialized nurse-led services can provide highly effective PICC placement with minimal need for physician or radiology support.

Regarding placement accuracy and procedural efficiency, IC-ECG systems have shown excellent outcomes across multiple studies. Previous reports described tip localization accuracy of up to 100%, while a review involving 729 patients found significantly greater placement accuracy compared with landmark-based methods (OR 8.3; $p = 0.02$). Malposition rates were low, with only 1% aberrant tip positions reported in one Sherlock 3CG study. In addition to accuracy, IC-ECG guidance shortened procedure time by approximately 13 minutes compared with fluoroscopy (31.8 vs 44.7 minutes). Time to therapy initiation was also substantially faster (33.9 vs 176.3 minutes) when compared with blind insertion followed by chest X-ray confirmation. Use of IC-ECG technology also reduced radiology dependence, with only 0.03 chest X-rays per patient required after Sherlock 3CG-guided placement compared with 1.25 per patient after blind insertion. One hospital further reported that 227 chest X-rays were avoided after implementation. Collectively, these findings support IC-ECG guidance as an accurate, efficient, and resource-saving approach for PICC placement.

Additional evidence for nurse-led vascular access services was reported in a retrospective study conducted at a university hospital in Japan between 2014 and 2020 (Sakai et al., 2024). Among 6,007 central venous access device placements, 2,230 PICCs were inserted, including 725 by physicians and 1,505 by nurse practitioners (NPs). Following implementation of the NP-led PICC programme, monthly CICC use significantly decreased from 58 to 38 cases, while NP-led PICC insertions increased from 0 to 104 per month. The programme significantly reduced both the immediate rate and long-term trend of CICC utilization. PICC placements performed by NPs were associated with lower immediate complication rates compared with physicians (1.5% vs 5.1%), while rates of central line-associated bloodstream infection (CLABSI) remained similar between groups (5.9% vs 7.2%). These findings suggest that NP-led PICC services can safely reduce reliance on more invasive central venous devices while maintaining comparable infection outcomes.

Further economic and organizational benefits were demonstrated at Hospital Clinic Barcelona in Spain, where implementation of a specialized VAT and intravenous therapy programme was evaluated during its first year of activity (Rosich-Soteras et al., 2025). During this period, the programme generated estimated savings of €867,688.44 through reduced material and labor force costs. Introduction of PICCs and midline catheters prevented insertion of 893 CICCs and 330 implantable venous ports, accounting for savings of €794,538.44. In addition, 34 patients who would otherwise have required hospitalization received treatment through the home hospital model, preventing 488 hospital days and generating a further €73,150 in savings. The programme was also clinically effective, achieving a first-attempt insertion success rate of 95.6%. Due to high service demand, VAT working hours were extended by 6.5 hours per day. An important component of the team's activity was consultation and education of other healthcare professionals, with 80.9% of consultations related to vascular access management, most commonly catheter occlusion. These results highlight the wider institutional value of VAT services in improving efficiency, reducing costs, and supporting safer vascular access care.

Additional European evidence was provided by the multicentre survey The state of vascular access teams: results of a European survey, which evaluated vascular access management across several European countries and included 1,449 healthcare professionals from public and private institutions (Rey et al., 2021).

The comparison between nurse-led PICC teams and physician-led insertion models has emerged as an important clinical and organizational question. Understanding differences in insertion success, complication rates, timeliness of care, catheter tip accuracy, and overall healthcare efficiency is crucial for hospitals seeking to design optimal vascular access services. In response to the increasing demand for reliable venous access, the growing use of PICC and midline catheters, physician workload pressures, and the need for ultrasound-guided insertion expertise, specialized VAT were developed (Fernandez-Fernandez et al., 2024). These teams were also established to prevent catheter-related complications and to implement standardized pathways for catheter insertion and maintenance. In many healthcare institutions, VAT are nurse-led and operate across both inpatient and outpatient settings, providing comprehensive catheter management throughout the entire device lifecycle.

Dedicated VAT models have been associated with improved organizational efficiency, faster access to treatment, and better patient outcomes. By offering rapid bedside availability, scheduled service coverage, fewer referrals to radiology, standardized documentation, and integrated follow-up care, nurse-led teams can reduce delays in therapy initiation, imaging, antibiotic administration, and hospital discharge (Freitas et al., 2026).

Insertion success is considered a key quality indicator of vascular access services. A 2024 retrospective cohort study from Saudi Arabia, a nurse-led PICC service reported an overall successful placement rate of 99.1%, with most catheters inserted using IC-ECG tip confirmation rather than fluoroscopy (Alsaleh et al., 2025). Similarly, comparative data from a Japanese university hospital involving 2,230 PICCs demonstrated that nurse practitioner-led placement quality was equivalent or superior to physician-led insertion, with lower immediate complication rates in the nurse-led group (Sakai et al., 2024). These findings suggest that successful outcomes are strongly associated with training, procedural volume, and dedicated practice rather than professional background alone.

The concept of IC-ECG was first described in 1949, when Hellerstein, Pritchard, and Lewis demonstrated the recording of intracardiac electrical potentials through a saline-filled catheter (Hellerstein et al., 1949). This principle later formed the basis of modern IC-ECG tip confirmation systems, which allow bedside verification of central venous catheter tip location without exposure to ionizing radiation (Tomaszewski et al., 2017). The technique is based on analysis of P-wave morphology, where progressive changes in the P wave indicate the catheter tip approaching the Cavo atrial junction. Increasing evidence supports IC-ECG as a safe, accurate, and efficient method of tip confirmation, with recent meta-analyses demonstrating advantages over traditional blind insertion techniques which includes X-ray confirmation and favourable cost-effectiveness (Liu et al., 2019).

Advanced tip confirmation systems combine electromagnetic navigation with real-time IC-ECG guidance, enabling simultaneous catheter tracking and accurate tip localization during insertion (Pittiruti et al., 2021). This technology allows immediate bedside confirmation of correct catheter tip position without the need for post-procedural chest radiography or fluoroscopy. The integration of IC-ECG systems within specialized VAT provides several important clinical and organizational benefits. Afore mentioned system points to higher first-attempt and overall insertion success rates, improved catheter tip accuracy, fewer malposition's and mechanical complications, as well as reduced dependence on fluoroscopy and chest radiography confirmation. Consequently, radiation exposure for both patients and healthcare staff may be minimized.

In addition, IC-ECG guided insertion is associated with shorter procedure times and faster catheter readiness for therapy, allowing earlier initiation of treatment. From an organizational perspective, this model can reduce physician procedural workload, decrease radiology utilization, and lower associated healthcare costs (Robinson et al., 2005). Because VAT often manage the catheter pathway from insertion through maintenance, they may also improve continuity of care, patient education, and overall patient experience.

Economic evaluations further support this model. Freitas et al. (Freitas et al., 2026) demonstrated that VAT utilizing IC-ECG based tip confirmation systems for PICC insertion improved procedural efficiency while reducing costs related to treatment delays, imaging requirements, and workflow burden. Overall, current evidence suggests that VAT equipped with IC-ECG technology represent an effective modern model of PICC service

delivery, combining clinical safety, procedural efficiency, patient-centred care, and economic benefit (Pinelli et al., 2025).

Results showed that the availability of dedicated VAT varied considerably between countries and hospitals. Institutions with an established VAT were more likely to use formal algorithms or guidelines for vascular access device selection (55% vs. 38%; $p < 0.0002$), as well as to systematically monitor complications and receive structured feedback (40% vs. 28%; $p = 0.015$).

Education was one of the most significant differences, as respondents from hospitals with a VAT reported higher rates of vascular access training (79% vs. 53%; $p < 0.0001$).

The study also identified barriers to VAT development, including unequal service availability, differences between hospital types, and the need for standardized education and competency frameworks.

Overall, findings from Saudi Arabia, Japan, and Spain consistently demonstrate that specialized nurse-led PICC and VAT can deliver safe, accurate, and efficient catheter placement. Implementation of IC-ECG guidance improved catheter tip confirmation, shortened procedure duration, reduced delays to treatment, and lowered use of chest X-ray or fluoroscopy. Such models reduce dependence on physicians and radiology services, lower complication rates, optimise use of vascular devices, and generate substantial organizational and financial benefits. Hospitals with vascular access teams also reported workflow benefits, lower costs, and improved continuity of care.

4. Discussion

Despite favorable findings, the current evidence base has several important limitations. Many published studies are retrospective observational analyses, which increase the risk of selection bias and confounding factors compared with randomized controlled trials (Pittiruti et al., 2020). Many positive findings regarding nurse-led PICC teams are based on retrospective cohort studies rather than randomized trials (Alsaleh et al., 2025). A limitation of the study's is that the survey responses were predominantly provided by nurses, which may have influenced the findings and may not fully reflect the perspectives of other healthcare professionals involved in vascular access management. In addition, retrospective data collection may rely on incomplete clinical documentation, leading to underreporting of adverse events.

Another limitation is the relatively small number of randomized comparative studies and the frequent absence of a true control group. Many investigations evaluate nurse-led services as single-arm cohorts without direct comparison to physician-led models under equivalent conditions, making causal interpretation more difficult (Liu et al., 2019). Simpler cases may be allocated to VAT nurses, whereas more complex patients are referred to physicians or interventional radiologists, introducing selection bias (Paje et al., 2023).

Variation in scope-of-practice legislation, credentialing systems, training standards, and operator experience may also affect the applicability of results across institutions and countries. Furthermore, studies often include heterogeneous patient and catheter populations and are frequently conducted in single-center settings, which may limit generalizability (Pittiruti et al., 2020). Although previous studies have also reported notable PICC related complication rates, current evidence suggests that outcomes improve significantly within VAT models led by expert nurses (McDiarmid et al., 2017).

Therefore, direct comparisons between professions should be interpreted cautiously, and further multicenter randomized studies with standardized methodology are needed.

5. Conclusions

Current evidence suggests that VAT represent an effective and progressive model of PICC service delivery. Multidisciplinary VATs involving specially trained nurses, physicians, and advanced practitioners can achieve clinical outcomes comparable to, and in selected settings better than, traditional physician-led insertion models. Studies have consistently reported high insertion success rates, low complication rates, shorter waiting times, improved clinical workflow efficiency, and better continuity of patient care.

Importantly, the literature indicates that the most significant determinants of procedural quality are training, competency, experience, and adherence to standardized evidence-based protocols, rather than professional background alone. This supports a competency-

based approach in which appropriately trained clinicians perform vascular access procedures according to institutional governance and patient needs.

Looking ahead, VAT services are likely to play an increasingly important role in modern healthcare systems. Future developments may include AI-assisted ultrasound vein mapping, advanced tip confirmation technologies, nurse consultant-led services, formal advanced practice credentialing pathways, international outcome benchmarking, and tele-supervision supported by simulation-based education. These innovations may further improve procedural safety, access efficiency, workforce flexibility, and patient-centered care.

Overall, the survey suggests that VAT services improve staff education, adherence to evidence-based practice, and complication surveillance, although wider implementation and further standardization are still needed across Europe.

However, further multicenter prospective studies are needed to compare service models, define optimal staffing structures, and evaluate long-term clinical and economic outcomes. Overall, healthcare organizations should prioritize development of high-quality VAT programs that combine multidisciplinary collaboration, advanced technology, and standardized competency frameworks to ensure safe and timely vascular access care.

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Research

Medial Discoid Meniscus Tear Treated with Platelet-Rich Plasma: A Case Report

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Abstract:
Discoid medial meniscus is a rare developmental variant associated with structural abnormalities that increase susceptibility to injury. The case of a 12-year-old boy with left knee pain following a direct blow is presented. Initial magnetic resonance imaging revealed a discoid medial meniscus without a clear tear, accompanied by oedema at the meniscocapsular junction. Despite conservative management, including physiotherapy, symptoms persisted, and a platelet-rich plasma injection was administered. The patient experienced temporary pain relief; however, symptoms recurred after eight months, and follow-up magnetic resonance imaging demonstrated progression of the lesion. Due to clinical deterioration, arthroscopic intervention was performed, revealing peripheral instability, which was treated with meniscocapsular stabilization. This case highlights that platelet-rich plasma may provide short-term symptomatic relief in discoid medial meniscus but does not prevent progression of underlying structural pathology. Its anti-inflammatory and analgesic effects may mask mechanical instability, potentially delaying definitive treatment. Careful clinical and imaging follow-up is therefore essential. The role of platelet-rich plasma in meniscal injuries, particularly as a stand-alone conservative treatment, remains uncertain. Further studies are needed to determine optimal treatment protocols and long-term outcomes.

Keywords: Discoid medial meniscus; Platelet-rich plasma; Meniscal injury; Pediatric patient; Conservative treatment

1. Introduction

The meniscus plays a crucial role in the biomechanics of the knee joint (Saavedra et al., 2020). Discoid meniscus (DM) is a rare developmental variant of meniscal growth and development. The tissue of a DM is hypertrophic, with a reduced content of collagen fibers and a more disorganized fiber orientation compared to a normal meniscus. Instead of the typical crescent form, a DM is thicker and wider, and in some cases may cover an entire half of the tibial plateau. These structural differences increase the susceptibility of the DM to tears due to shear forces. Even in the absence of tears, its size and shape alone may restrict joint motion. When symptomatic, it can cause pain and limit mobility in otherwise healthy and active children (Anderson et al., 2023). Prolonged pain (> 6 months) due to a tear doubles the risk of associated chondral lesions (Saavedra et al., 2020). The clinical presentation of DM is highly variable and depends on several factors, including the shape and stability of the meniscus, concomitant intra-articular pathologies, as well as the patient's age and level of physical activity (Saavedra et al., 2020; Albishi et al., 2024). The most common symptoms include episodic pain, swelling, joint snapping, and mechanical locking; additionally, a characteristic "click" may be heard during terminal knee extension (Albishi et al., 2024).

The pathogenesis of DM remains a matter of debate (Chen et al., 2013). Its prevalence is notably higher in Asian populations (Saavedra et al., 2020). Most of the current knowledge is based on studies of the more common discoid lateral meniscus, with a reported prevalence ranging from approximately 0.4% to 20% (Anderson et al., 2023) or 1.5% to 15% (Chen et al., 2013), depending on the population and sampling method. In contrast, the discoid medial meniscus (DmM) is exceedingly rare, with an estimated prevalence between 0.06% and 0.3%, depending on the studied population. The literature regarding its clinical presentation, surgical treatment, and outcomes is limited (Anderson et al., 2023).

Initial diagnostic evaluation includes standard radiography and magnetic resonance imaging (MRI) (Accadbled et al., 2025; Saavedra et al., 2020), while arthroscopy provides definitive confirmation of meniscal morphology and stability (Saavedra et al., 2020). Current recommendations classify DM based on morphology (complete/incomplete), peripheral stability (stable/unstable), and the presence of a tear. The goal of treatment is to restore typical anatomy through saucerization, management of tears, stable meniscal fixation, and repair of unstable peripheral rims (Anderson et al., 2023; Saavedra et al., 2020).

1.1 Platelet-rich plasma

Platelet-rich plasma (PRP) is blood plasma with a platelet concentration higher than baseline levels. In addition to platelets, it contains coagulation factors and is enriched with growth factors, chemokines, cytokines, and other plasma proteins (Alves & Grimalt, 2018, Troha et al., 2023). The role of platelets in tissue healing processes has stimulated extensive research and led to their therapeutic application in musculoskeletal disorders, particularly in cartilage pathologies and degenerative meniscal injuries (El Zouhbi et al., 2024; Mitev & Longurov, 2019; Xie et al., 2014). Due to its autologous origin, PRP reduces the risk of adverse effects and represents a simple, effective, and cost-accessible therapeutic approach (El Zouhbi et al., 2024).

The aim of this case study is to present a rare case of DmM and to examine the role of PRP in its treatment, particularly considering the potential discrepancy between subjective symptom improvement and the actual morphological progression of the lesion.

2. Case presentation

A 12-year-old boy was referred to a traumatologist for evaluation of pain in the left knee. He reported a direct blow to the knee that resulted in swelling and pain. The condition improved after a few days; however, three months later, pain recurred in the medial aspect of the knee, primarily during increased physical load and prolonged standing. The patient denied any prior knee injuries. Written informed consent for the publication of this case report and any accompanying clinical data or images was obtained from the patient's parents. Every effort has been made to ensure the anonymity of the patient. A copy of the written consent is available for review by the authors.

Plain radiography demonstrated a skeletally immature knee with open growth plates, without evidence of fractures or dislocations. MRI revealed a DmM with centrally increased signal intensity without evidence of a tear, along with mild edema at the meniscocapsular junction and in the posteromedial portion of the tibial epiphysis (**Figure 1A**). On clinical examination, there was tenderness to palpation over the medial joint line, corresponding to the area of meniscocapsular oedema observed on MRI. The range of motion of the left knee was preserved. Ligamentous structures were stable and comparable to the contralateral side. The Ballottement and McMurray tests were negative.

3. Treatment

Following the initial clinical and imaging evaluations, rest was recommended, along with avoiding excessive strain on the knee joint and activities that provoked pain. Participation in sports activities was also discouraged while the pain persisted. Since the condition did not improve significantly within a month, the patient was referred to physical therapy. He underwent an individually tailored exercise program, with an emphasis on muscle strength training and analgesic electrostimulation. He also received instructions on the proper execution of the exercises at home. After completing physiotherapy, the patient reported partial pain relief, along with improved muscle strength.

As the pain persisted, a decision was made during a follow-up examination to perform an ultrasound-guided PRP injection (using the double centrifugation method, i.e., "leucocyte-poor" PRP using the Arthrex ACP Max method). It was applied at the site of greatest tenderness in the meniscocapsular junction of the medial meniscus, with the purpose of locally stimulating tissue regeneration. Following the application, the patient was advised to adjust physical activity according to pain levels and gradually return to sports activities as symptoms improved. No physical therapy was performed in the period following the PRP application, as this could have masked its therapeutic effect.

Immediately after the PRP application, the patient reported intense pain (VAS = 8/10), which subsided within one week. The temporary increase in symptoms immediately after injecting PRP can be attributed to the method of administration; specifically, following application to the periphery of the meniscus (extra-articular), more intense pain may be present compared to intra-articular application, similar to what can be observed in intra-meniscal application. In intra-meniscal application, pain lasts an average of 2–3 days and may result from increased pressure that develops in the tissue during infiltration (Sánchez et al., 2023).

4. Outcomes

Three months after the PRP injection, the patient reported a reduction in pain. The pain was present only during high impact activities. The patient and his parents were satisfied with the results, so the therapy was deemed successful. At this point, the treatment was concluded. Eight months later, knee pain recurred, so the patient was referred for second MRI (**Figure 1B**). A horizontal fissure was identified, seemingly extending across the entire surface of the meniscus and most likely disrupting the inferior articular surface in the posterior portion. A small parameniscal cyst in the body region and a slightly dysplastic medial femoral condyle were also detected. Initially, conservative treatment was pursued; however, due to the aggravation of symptoms and progression of structural changes visible on the imaging, the decision to proceed with operative treatment was made. Knee arthroscopy was indicated.

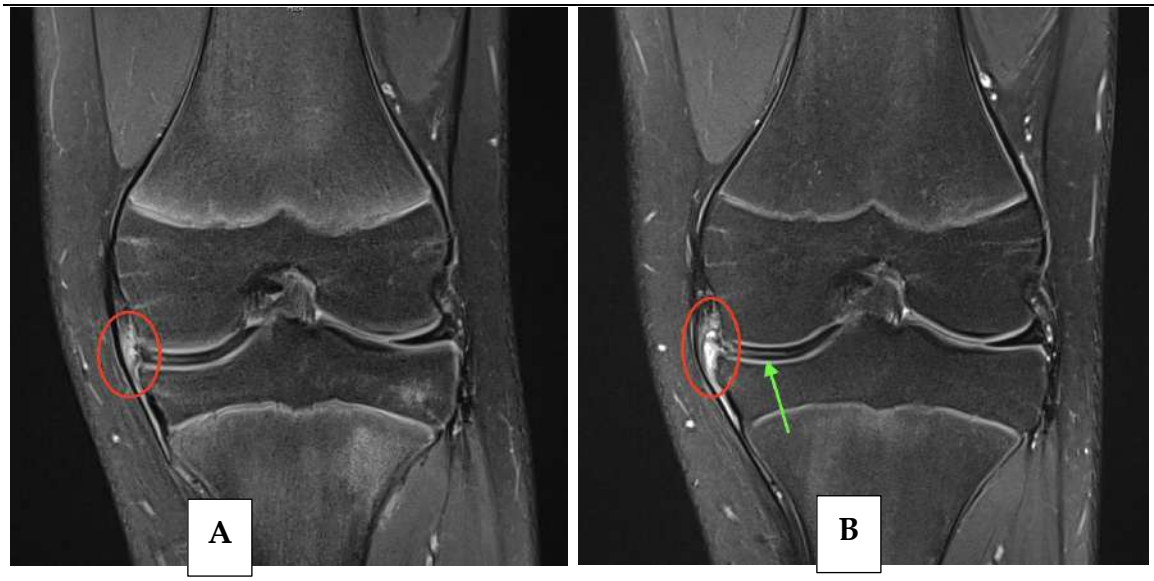

Figure 1. A: The red ellipse indicates the site of the edema and a suspected injury to the ligamentous structures at the peripheral aspect of the discoid medial meniscus (7. 9. 2024). B: The red ellipse indicates the site of the progression of edema at the periphery of the medial meniscus. The green arrow indicates the progression of horizontal separation of the meniscus into the upper (femoral) and lower (tibial) surfaces (2. 2. 2026).

During the arthroscopic procedure, no visible signs of meniscal degeneration or tear were observed. Given the preserved meniscal tissue and the absence of significant degenerative changes in the articular surfaces, saucerization was not performed. A site of relative weakness with increased meniscal mobility was palpated at the periphery of the meniscus. At this site, a suture was placed using the "all-inside" technique (Arthrex FiberStitch) to reinforce the meniscocapsular junction. Postoperatively, relative rest and avoiding knee flexion beyond 90° were recommended. At the follow-up examination two weeks later, the knee was not swollen, and passive knee range of motion was adequate. Palpation of the medial aspect of the knee did not elicit significant pain. The patient was advised to walk normally and was also referred to physiotherapy.

5. Discussion

Most cases of DM are asymptomatic and do not require treatment, as the knee joint likely adapts to the altered anatomy and maintains adequate function (Kim et al., 2016). Due to the rarity of DmM cases, treatment recommendations are limited (Accadbled et al., 2025). Yang and colleagues (2022) cite three indications for a conservative approach: if the lesion is asymptomatic and discovered incidentally; if clinical signs are mild and do not affect daily activities or regular sports activities; and if symptoms are present due to another comorbid condition (e.g., osteoarthritis, rheumatoid arthritis). Physiotherapy is also recommended as a conservative approach, although there is no evidence that exercise maintains DM in an asymptomatic state (Albishi et al., 2024). Conservative treatment of symptomatic DM has a high failure rate in the literature (Logan et al., 2021). Logan and colleagues (2021) found that, out of 83 cases of conservatively treated DM, 39% required additional surgical treatment.

Surgical treatment is indicated in cases of symptomatic ruptures, instability, or chronic pain (Accadbled et al., 2025; Saavedra et al., 2020). DmM is generally considered a congenital anomaly (Flouzat-Lachaniette et al., 2011), characterized by structural changes such as a disorganized collagen network, mucinous degeneration, and reduced vascularization, which increases its susceptibility to injury even without significant trauma (Saavedra et al., 2020). In our case, the patient reported a direct blow to the knee, which likely triggered symptoms in a previously asymptomatic meniscus, raising the possibility of a traumatic etiology. In our interpretation this most likely represents a lesion of the DmM periphery, that would not typically occur in a normally structured meniscus suggesting a mixed traumatic-degenerative etiology, to which the discoid nature of the meniscus very likely contributed. Given the subtle changes on MRI, a conservative

treatment regimen was initially prescribed, but it did not yield satisfactory improvement. PRP therapy was subsequently indicated with the aim of stimulating regenerative processes in the menisco-capsular junction, where pain was clinically most evident alongside concomitant MRI-visible changes (oedema).

Although PRP is increasingly used for various musculoskeletal conditions, its role in meniscal injuries is largely limited to adjunctive therapy during surgical procedures and is less commonly used as a primary conservative treatment (Sánchez et al., 2023). In the present case, when PRP was indicated, the clinician believed that the lesion was not mechanically unstable and that stimulating local healing processes could help alleviate symptoms. However, it turned out that the meniscal lesion assessed as mechanically unstable could not be treated exclusively with PRP.

Ishida et al. (2007) found that PRP enhances the healing capacity of the inner, avascular portion of meniscal cells, likely due to growth factors that enhance the biological activity of meniscal cells and promote tissue regeneration. In an in vivo model of meniscal injuries in rabbits, the newly formed reparative fibrocartilaginous tissue was structurally similar to the inner parts of the normal meniscus, although histologically, boundaries between the regenerated and healthy tissue were still visible (Ishida et al., 2007).

Despite improved functional outcomes in patients with degenerative meniscal tears who received PRP, no evidence of lesion healing was visible on MRI, which could be explained by its isolated anti-inflammatory effect, the differing MRI signal characteristics of scar tissue, or the relatively short follow-up period (Guenoun et al., 2020). Similarly, in our case the temporary efficacy of PRP therapy could be attributed to its anti-inflammatory effect, while the mechanical lesion at the periphery of the DmM progressed and was more pronounced on the follow-up MRI. The situation could therefore be interpreted as PRP masking the symptoms of otherwise progressive mechanical lesion at the periphery of the DmM.

In adolescents with meniscal injuries, intra-articular PRP injection has been shown to be effective in reducing pain (Popescu et al., 2020). However, a study on discoid lateral meniscus injuries showed no difference in clinical outcomes between the PRP group and the non-PRP group (Dai et al., 2019). In the described case, PRP administration successfully provided temporary pain relief but was unable to stimulate reparative processes to the extent required for healing of the meniscal lesion. Furthermore, once the anti-inflammatory effect of PRP therapy wore off, symptoms recurred after nearly one year.

The presented case demonstrates that conservative treatment of DmM with PRP can lead to temporary improvement in symptoms but does not prevent or reverse the underlying structural changes in the meniscus. The PRP injection resulted in a temporary reduction in pain, which allowed the patient to engage in a higher level of activity. Nevertheless, a single PRP application could not induce significant morphological healing, which was later reflected in the progression of the lesion and the need for arthroscopic surgical intervention. Despite promising results from experimental models suggesting the regenerative potential of PRP (Ishida et al., 2007), the findings of clinical studies are inconsistent. Dai et al. (2019) found that the addition of PRP during arthroscopic suturing of the discoid lateral meniscus does not reduce pain or contribute to improved function compared to standard surgical treatment without added PRP. Sánchez and colleagues (2023), however, report that the combination of intrameniscal and intra-articular PRP applications represents an effective conservative treatment method for meniscal injuries that may reduce the need for surgical intervention.

In the case described, physiotherapy was not included following PRP administration to isolate the effect of PRP; however, this may represent a limitation from the perspective of comprehensive DM management. In literature, PRP is often used in combination with physiotherapy treatment. Kaminski et al. (2019) demonstrated that the combination of percutaneous trepanation, PRP and targeted physiotherapy improves clinical outcomes and reduces the need for subsequent surgical treatment. The lack of concomitant physiotherapy may have limited the extent of functional improvement observed in this case. The synergistic effect of the combined approach remains unclear and warrants further investigation.

At the same time, questions remain regarding the optimal protocol for PRP use, including the potential need for repeated applications and the duration of the follow-up after PRP administration, as most studies are based on the short-term outcomes. In our case, PRP did

not provide lasting improvement. Symptoms worsened, necessitating surgical intervention with arthroscopic meniscal stabilization.

6. Conclusions

DmM is a rare, often asymptomatic anatomical condition that can pose a significant diagnostic and therapeutic challenge. The presented case confirms the ambivalent effect of PRP in clinical practice—on the one hand, it can serve as an effective symptomatic therapy and potentially delay surgical treatment; on the other hand, due to the absence of a structural effect, it may contribute to underestimating the underlying pathology. As demonstrated in this case, symptomatic improvement may mask progression of an underlying mechanical lesion, emphasizing the importance of careful clinical and imaging follow-up. Given the variability in application protocols and inconsistent evidence regarding long-term outcomes, PRP should be used selectively and on an individual basis, with consideration of its cost-effectiveness. Since this is a presentation of a single case report, the findings cannot be generalized; however, they may contribute to a better understanding of the role of PRP in the treatment of meniscal injuries.

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Research

Physiotherapy Approach in Linear Scleroderma of the Lower Limb: A Case Report

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Abstract:
Linear scleroderma is a subtype of localized scleroderma that may affect deeper tissues, including fascia and muscle, leading to joint restriction, gait abnormalities, and functional impairment. Evidence based physiotherapy management in these patients remains limited. We report the case of a 17-year-old female with juvenile linear scleroderma affecting the left lower limb, involving dermatomes L3–L4 and fibrosis of the *m. Sartorius*, *m. Rectus femoris*, and *m. Vastus lateralis*. Previous medical treatment included systemic corticosteroids and methotrexate; however, long-term functional progress was limited, and treatment tolerance was poor. Before initiation of our physiotherapy intervention, no clearly visible functional or structural improvement had been documented. A five-month individualized physiotherapy program was delivered once weekly (60 minutes/session). Treatment consisted of myofascial release, manual therapy, proprioceptive neuromuscular facilitation, dry needling, static and dynamic cupping therapy, strengthening exercises, movement re-education, and a home exercise program including foam rolling. Following intervention, clinically meaningful improvements were observed in hip and knee mobility, lumbopelvic movement control, gait symmetry, and overall functional performance. Soft tissue quality improved, with reduced induration, increased mobility, and decreased visible contour irregularities of the affected thigh. The patient also reported improved well-being and easier participation in daily and sports activities. No worsening of disease status was observed during the treatment period. This case suggests that individualized physiotherapy may be an effective adjunctive treatment approach in juvenile linear scleroderma of the lower limb. Further research is required to determine optimal rehabilitation strategies and long-term outcomes.

Keywords: Linear scleroderma; Localized scleroderma; Morphea; Lower limb; Physiotherapy

1. Introduction

Scleroderma is a rare connective tissue disease characterized by skin thickening and induration resulting from excessive deposition of collagen and other extracellular matrix components, such as fibronectin, proteoglycans, and glycosaminoglycans. In systemic sclerosis, also known as progressive systemic sclerosis or generalized scleroderma, symmetrical skin thickening is often accompanied by internal organ involvement, which may lead to serious and potentially life-threatening complications. Localized scleroderma (morphea) represents a distinct clinical form of the disease characterized by an asymmetrical process of skin thickening and induration. The changes are usually confined to the skin. Recent studies suggest that, in certain cases, the localized form of the disease may also involve internal organs and is associated with varying degrees of clinical burden (Careta & Romiti, 2015; Falanga, 1989). Although the course of localized scleroderma is often relatively mild, the disease may cause permanent functional limitations and significant cosmetic deformities in some patients. Recognition of prognostic factors described in recent studies may substantially contribute to more appropriate management and treatment of these patients (Falanga, 1989).

1.1. Localized scleroderma

Morphea is characterized by skin thickening associated with increased collagen deposition within indurated lesions (Matsuura et al., 1997). Localized scleroderma is clinically classified into several subtypes, including circumscribed (limited) morphea, linear morphea, and generalized morphea. Extracutaneous manifestations are frequently present in patients, particularly in the juvenile form of the disease, and are associated with higher disease activity and reduced quality of life. Due to the complexity of the disease course, a multidisciplinary approach is often required in the management of these patients (Takahashi et al., 2025). Morphea usually follows a self-limited course, and spontaneous improvement may often occur within a period of 3 to 5 years. However, the risk of disease recurrence remains relatively high, even after a prolonged period of inactivity. This is particularly relevant in children with linear scleroderma or mixed forms of morphea, in whom long-term and careful clinical follow-up is essential (Asano et al., 2018; Careta & Romiti, 2015; Mertens et al., 2015). The clinical presentation of morphea is highly variable and includes several heterogeneous subtypes. Skin lesions may affect quality of life to varying degrees and, in some cases, may result in permanent physical and psychological consequences (Arkachaisri et al., 2010; Bielsa Marsol, 2013; Kroft et al., 2009). Owing to pain, fatigue, stigmatization, and the impact of the disease on daily life, together with reduced social support and acceptance, patients with morphea are at increased risk of developing psychological problems such as depression and anxiety (Kroft et al., 2009). Despite numerous available therapeutic options, treatment response varies among different morphea subtypes. Furthermore, there is still no clear consensus regarding the optimal choice of therapy, appropriate dosing, and treatment duration that would ensure good tolerability, minimal adverse effects, and maximum benefit for patients (Asano et al., 2018; Knobler et al., 2017; Zwischenberger & Jacobe, 2011).

1.2. Linear scleroderma

The linear subtype of scleroderma commonly occurs in children and young adults (Takahashi et al., 2025). Childhood-onset linear scleroderma is associated with a more severe clinical course compared with disease onset in adulthood (Asano et al., 2018). It is characterized by well-demarcated, unilateral linear or band-like sclerotic lesions, which are often slightly depressed and typically occur on the limbs, face, or scalp. The distribution of lesions frequently follows Blaschko's lines, supporting the hypothesis of a role for somatic mosaicism in disease pathogenesis. Lesions may extend into deeper tissues, potentially leading to atrophy of the subcutaneous fat, muscles, tendons, and bone. When the limbs are affected, deformities and joint contractures may develop. In children, impaired growth of the affected limb is also commonly observed (Takahashi et al., 2025). Linear scleroderma involving the frontal or frontoparietal region, with or without associated hemifacial atrophy, is referred to as en coup de sabre morphea. Parry-Romberg syndrome is characterized by hemifacial atrophy in the absence of sclerotic skin changes (George et al., 2020). The disease primarily affects adipose tissue, although in some cases it may also

extend to the bones and muscles, resulting in marked atrophy of muscular and fatty tissues. In such cases, cutaneous manifestations may be minimal or absent (Tollefson & Witman, 2007).

1.3. Anatomical and pathological skin changes

In scleroderma, the histological appearance depends primarily on the stage of the disease and the depth of pathological tissue involvement. In most cases, morphological changes are most pronounced at the junction between the dermis and subcutaneous tissue; therefore, an adequate skin biopsy specimen should also include subcutaneous tissue for proper histological evaluation (Careta & Romiti, 2015). In the early inflammatory phase of the disease, or in initial lesions that clinically often present with an erythematous component, histological findings are not yet characteristic of scleroderma, which may make definitive diagnosis challenging. During this phase, increased density and homogenization of collagen fibers may be observed. Treatment usually includes local therapeutic approaches, immunosuppressive medication, physiotherapy, and phototherapy (Hunzelmann et al., 1998). Although the effectiveness of physiotherapy in patients with morphea has not yet been sufficiently investigated, currently available evidence suggests that physiotherapy does not worsen the course of the disease and may be beneficial in maintaining range of motion and preventing joint contractures (Fett & Werth, 2011). Treatment of localized scleroderma should be initiated as early as possible, before complications occur, as the disease may lead to limited mobility and the development of deformities due to its potentially high morbidity. Assessment of disease activity is essential when selecting an appropriate therapeutic approach. Disease activity is evaluated on the basis of several clinical and laboratory indicators. Important signs include the appearance of new lesions or progression of existing lesions within the previous three months, which should be documented by a physician. Moderate to severe erythema of the lesion, the presence of an erythematous or violaceous border, and increased induration at the margins may also indicate active disease. An important marker of disease activity is progression of lesions into deeper tissues, which can be confirmed using imaging modalities such as photography, magnetic resonance imaging, or ultrasound. In addition, worsening hair loss on the scalp, eyebrows, or eyelashes, elevated creatine kinase levels in the absence of other pathological findings, and skin biopsy results confirming active disease may also indicate disease activity. Clinical signs of permanent tissue damage may include dermal atrophy, subcutaneous tissue atrophy, skin pigmentation changes in the form of hyperpigmentation or hypopigmentation, and increased skin thickness in the center of the lesion (Careta & Romiti, 2015).

1.4. Assessment of skin changes in localized scleroderma

For a comprehensive evaluation of skin changes in localized scleroderma, the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) is used. This instrument enables separate assessment of disease activity and the degree of permanent tissue damage. Disease activity is evaluated using the Localized Scleroderma Skin Severity Index (LoSSI), which includes several clinical parameters such as the extent of involvement, degree of erythema, skin induration, and the appearance of new lesions or progression of existing ones. Individual features are scored on a standardized scale from 0 to 3 across eighteen anatomical sites. The modified version of the index (mLoSSI) does not include assessment of the affected surface area. The Localized Scleroderma Skin Damage Index (LoSDI) is calculated as the sum of scores for dermal atrophy, dyspigmentation, and subcutaneous tissue atrophy. The Physician's Global Assessment (PGA) is used to evaluate overall disease activity and the extent of damage. It is based on a 100-mm visual analogue scale (VAS) (Arkachaisri et al., 2009).

1.5. Treatment

The management of localized scleroderma has become increasingly standardized in recent years, with methotrexate established as the first-line systemic treatment for more severe forms of the disease (Takahashi et al., 2025). In the early inflammatory phase, corticosteroids are also frequently used and are usually prescribed in combination with methotrexate. After an adequate therapeutic response has been achieved, methotrexate treatment is generally continued for at least 12 additional months in order to reduce the risk of relapse (George et al., 2020). Commonly reported adverse effects of methotrexate include nausea, fatigue, headache, hair loss, and hepatotoxicity (Albuquerque et al., 2019). In patients who do not achieve a satisfactory response to this treatment, targeted therapies are increasingly

being considered as promising alternatives, including abatacept, tocilizumab, and Janus kinase (JAK) inhibitors (Takahashi et al., 2025). Mycophenolate mofetil is used as an alternative therapeutic option in patients in whom methotrexate is contraindicated or in those who fail to respond adequately to methotrexate (George et al., 2020). Reconstructive procedures also play an important role in the management of late sequelae of the disease. These include autologous fat grafting, which is used for the treatment of atrophic changes (Takahashi et al., 2025). Advances in the understanding of disease pathogenesis and the development of new therapeutic options are creating opportunities for more effective and targeted treatment strategies, which may significantly improve long-term outcomes in patients with localized scleroderma (Takahashi et al., 2025). It is important that management is individualized according to disease severity and extent, with particular attention given to the risk of restricted mobility and the development of deformities (Kreuter et al., 2007).

1.6. Orthopedic complications

Orthopedic complications are common in patients with linear scleroderma and require particular clinical attention. In one study, such complications were present in more than 51% of children, while joint contractures were reported in 88% of affected patients. Importantly, these changes developed despite the use of immunosuppressive therapy, highlighting the need for early orthopedic involvement in the management of these patients (Schoch et al., 2018). According to the German guidelines, functional surgical procedures should be performed only during the inactive phase of the disease, generally several years after disease activity has ceased. In addition, concurrent physiotherapy management is recommended (with the exception of the acute inflammatory phase), focusing on improving mobility, strengthening muscles, performing functional exercises, manual lymphatic drainage, and massage (Kreuter et al., 2016).

1.7. Role of Physiotherapy

Physiotherapy is frequently included in the comprehensive management of patients with localized scleroderma, particularly in the presence of restricted mobility and joint contractures (Fett & Werth, 2011; Kreuter et al., 2016). Current evidence suggests that physiotherapy does not negatively influence the course of the disease and may contribute to maintaining mobility and reducing the risk of contracture development (Fett & Werth, 2011). Physiotherapy therefore plays an important role in preserving patients' functional capacity and represents an essential component of long-term rehabilitation (Kreuter et al., 2016). Despite its frequent use in clinical practice, however, the effectiveness of physiotherapy in patients with localized scleroderma has not yet been adequately investigated, highlighting the need for further clinical studies (Zwischenberger & Jacobe, 2011).

2. Case presentation

We present the case of a 17-year-old female patient with juvenile linear scleroderma involving the left lower limb, corresponding to L3–L4 dermatomes, with fibrosis of the left thigh sartorius, rectus femoris, and vastus lateralis muscles. The patient and her legal guardians provided written informed consent for the use of clinical data, medical documentation, and clinical photographs for the preparation and publication of this case report. The disease followed a chronic course with periods of relative stability and recurrent exacerbations. The patient was followed for several years in rheumatology, orthopeadic, and pediatric outpatient clinics, and later received physiotherapy management. Earlier reports described localized induration of the skin and subcutaneous tissue with reduced soft tissue elasticity and movement limitations, primarily in the region of the left thigh and hip.

The first available specialist reports from 2021 described linear scleroderma with muscular fibrosis and reduced mobility of the left lower limb, although without significant pain or major impact on daily functioning. During an orthopedic examination in March 2021, tension along the quadriceps was noted during flexion of the left knee in the prone position, with compensatory pelvic tilt and movement restriction in the left hip, despite otherwise favorable functional status and a normally performed squat. Radiographic findings described compensatory deviation at the thoracolumbar junction, associated with lower limb asymmetry or the functional consequences of limited hip mobility. At that time, the clinical assessment suggested substantial improvement, although continued follow-up during growth was considered necessary.

In the following years, the patient remained physically active and free of significant pain; however, compensatory movement patterns gradually became more pronounced during growth. Reports from 2022 and 2023 described limited flexion of the left knee, reduced rotation of the left hip, spinal compensations during provocative movements, and movement asymmetry. At the same time, the patient did not report major difficulties in school or sports activities, although structural and functional changes indicating progression of the disease into deeper tissues were clinically present. Additional imaging was therefore indicated in 2023.

MRI of the left thigh in March 2023 confirmed involvement of deeper soft tissues. Changes in the subcutaneous tissue with propagation toward fascial and muscular structures were described, together with signs of fibrotic and/or inflammatory changes in the affected region. The MRI findings served as an important basis for further therapeutic decision-making, as clinical examination alone only partially reflected disease activity. Subsequent outpatient follow-ups repeatedly emphasized that the inflammatory process could not be reliably assessed on the basis of clinical findings alone, and that a combination of clinical examination and imaging was required.

In 2024, reports again described tissue tightness and reduced extensibility in the region of the left thigh and gluteal area, the appearance of striae, and persistent limitation of specific movements, particularly during flexion of the left knee in the prone position, which provoked compensatory adjustments of the pelvis and spine. Despite this, the patient remained free of persistent pain and physically active. At examination in March 2024, she was able to perform a squat; however, specific movements still triggered lumbopelvic compensations, and reduced hip rotation was noted. The condition was considered clinically stable, although continued monitoring was recommended due to the risk of further fibrosis and functional deterioration.

Due to clinical worsening, the patient was hospitalized in December 2024 for a second cycle of pulse corticosteroid therapy and was readmitted in January 2025 for a third treatment cycle. During these admissions, documentation described firmness and tightness of the affected left thigh, the appearance of new striae, and persistent restricted mobility, especially during specific movements, although overall somatic status remained stable. Ultrasound examination of the soft tissues did not demonstrate significant structural differences between sides. Laboratory testing on admission in January 2025 revealed elevated transaminases and aldolase levels, which began to decline by discharge. The discharge report noted clinical softening of the affected area, continuation of methotrexate and folic acid, and consideration of additional systemic therapy if disease activity persisted.

Physiotherapy represented an important part of management. A physiotherapy report from January 2025 described markedly restricted mobility of the left hip, particularly in flexion and rotation, and the need to maintain mobility of the hip and lumbopelvic region. Treatment focused on active mobility exercises, pelvic and trunk stabilization, breathing exercises, activation of the tensor fasciae latae, bridging exercises, and hip abduction exercises. At the final physiotherapy assessment during hospitalization, it was noted that the patient demonstrated good axial stabilization control, that major gait asymmetries were no longer present, and that she was able to correctly perform hip abduction exercises. Mild limitations remained in hip–trunk dissociation and internal hip rotation. Continuation of the home exercise program and further progression of the rehabilitation program at future follow-ups were recommended.

Based on the overall documentation, it can be concluded that the patient had a long-standing course of juvenile linear scleroderma of the left lower limb with marked soft tissue involvement, functional impact on lower limb movement and the lumbopelvic region, and episodes of clinical deterioration requiring intensified systemic treatment. Despite the absence of persistent pain, the clinically significant issues were restricted mobility, development of compensatory movement patterns, and the risk of progressive fibrosis, which justified long-term multidisciplinary follow-up and inclusion of targeted physiotherapy management.

3. Treatment

Following review of the available medical documentation, no clearly visible functional or structural improvement had been documented prior to the beginning of our physiotherapy intervention. Therefore, a targeted physiotherapy program was initiated and continued for five months, with sessions performed once weekly, each lasting approximately 60 minutes.

The intervention combined manual therapy, myofascial techniques, proprioceptive neuromuscular facilitation (PNF), dry needling, and cupping therapy. Cupping was applied both statically and dynamically during movement tasks. Dynamic cupping was primarily used in quadruped positions with active movement, especially in the lumbosacral and gluteal regions.

During the treatment process, it was observed that the patient responded best to low-intensity, non-aggressive therapeutic techniques. More intensive interventions occasionally provoked an adverse or protective tissue response. For this reason, subsequent sessions were based predominantly on gentler manual and fascial approaches, with gradual progression according to tolerance.

The main treatment goals were to improve mobility of the hip, knee, and lower back, reduce gait asymmetry, optimize movement patterns, and improve tissue quality. Particular emphasis was placed on myofascial release, which produced the most noticeable clinical changes. Improvements in tissue extensibility and softening of previously indurated areas were already visible during the first month of treatment and continued throughout the intervention period. Previously pronounced depressions and irregularities of the affected thigh became less visible over time.

The rehabilitation program also included strengthening exercises, particularly targeting the gluteus medius, gluteal muscle group, and *m. transversus abdominis*. In addition, the patient was instructed to perform regular self-myofascial release using a foam roller between sessions, which appeared to contribute positively to maintaining treatment effects.

Overall, the intervention combined static soft tissue treatment with dynamic movement-based techniques, with a primary focus on fascial and myofascial structures, functional mobility, and neuromuscular control.

4. Outcomes

After five months of regular physiotherapy management, clinically significant functional and structural improvements were observed. The most pronounced progress was noted in the mobility of the left lower limb and the lumbopelvic region. Range of motion in the hip and knee increased noticeably, while compensatory movements of the pelvis and lumbar spine during previously restricted movements were reduced.

Improvement was also evident in gait, with reduced asymmetry of the movement pattern and enhanced overall functional movement control. The patient reported easier performance of daily activities, as well as an improved sensation during walking and physical activity.

Important changes were also observed in soft tissue quality. On palpation, the tissue of the affected left thigh was softer, more elastic, and more mobile compared with the initial condition. Previously marked areas of induration gradually softened, while visible depressions, irregularities, and thickening in the affected region became less pronounced. The lesion margins became less distinct and more mobile. Visual comparison of photographs taken before the start of treatment (**Figure 1**) and after five months (**Figure 2**) demonstrated noticeable improvement both on the anterior aspect of the thigh and in the gluteal and supragluteal regions.

Subjectively, the patient reported marked improvement in overall well-being, greater relaxation of the leg, and a sensation of increased mobility. No clinical deterioration or development of new limitations occurred during the treatment period.

Based on the observed changes, it may be concluded that individually tailored physiotherapy management focused on myofascial structures, improvement of mobility, and functional stability significantly contributed to the improvement of clinical status and functional abilities in this patient.

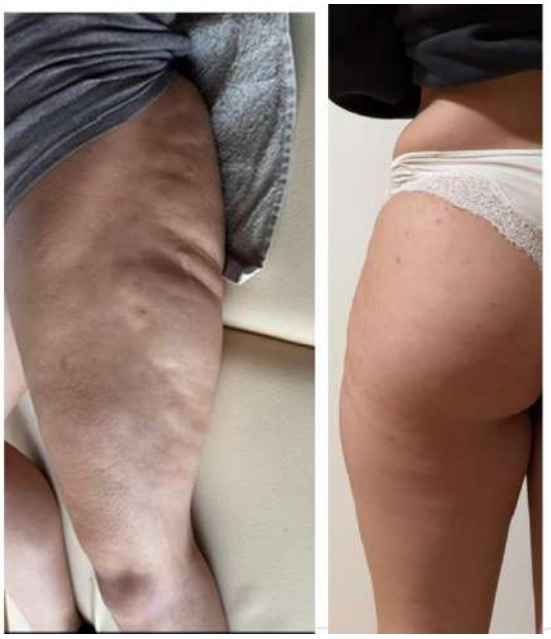

Figure 1. Clinical appearance of the affected left lower limb before physiotherapy intervention. The images demonstrate visible soft tissue asymmetry, contour irregularities, and tissue induration associated with juvenile linear scleroderma. On the anterior aspect of the thigh, multiple depressions and irregular soft tissue changes are visible. The posterior view demonstrates asymmetry and prominent contour changes in the gluteal and supragluteal region, corresponding to fibrosis and reduced soft tissue mobility identified during clinical examination.

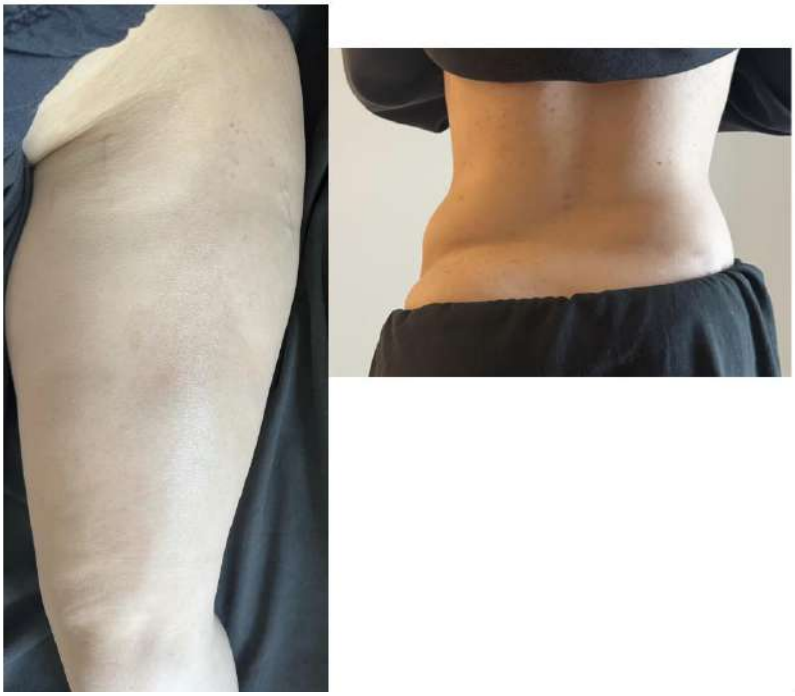

Figure 2. Clinical appearance of the affected left lower limb after five months of physiotherapy intervention. The follow-up images demonstrate improved soft tissue symmetry and reduced contour irregularities of the left thigh and gluteal region. Compared with the initial presentation, the previously prominent depressions and tissue protrusions are less pronounced, and the overall appearance of the soft tissues is smoother and more symmetrical. Clinical examination also revealed improved tissue mobility and reduced induration following physiotherapy management.

5. Discussion

The presented case demonstrates the clinically significant potential of physiotherapy management in a patient with juvenile linear scleroderma of the left lower limb, who presented with long-standing mobility restrictions, soft tissue changes, and compensatory movement patterns. Despite previous specialist follow-up and systemic treatment, no clearly visible functional improvement had been observed prior to the initiation of our intervention. In contrast, after five months of individually tailored physiotherapy, noticeable improvements were seen in mobility, tissue quality, gait, and the patient's subjective well-being.

Linear scleroderma is a subtype of localized scleroderma in which deeper tissues, including the subcutaneous tissue, fascia, muscles, and bone, are frequently affected, potentially leading to contractures, deformities, and functional limitations (Takahashi et al., 2025). When the lower limb is involved, gait disturbances, reduced joint mobility, and the development of compensatory movement patterns are particularly common. This is consistent with our case, in which limitations of the hip and knee, together with lumbopelvic compensations, were present. Such changes further support the importance of early and continuous rehabilitation management in this patient population (Schoch et al., 2018).

Available literature indicates that physiotherapy is frequently included as a supportive component of multidisciplinary management in patients with morphea, primarily with the aim of preserving mobility, preventing contractures, and improving functional capacity (Fett & Werth, 2011; Kreuter et al., 2016). However, evidence regarding its effectiveness remains limited due to the lack of high-quality randomized studies and standardized treatment protocols. Most current recommendations are based on clinical experience, small case series, and expert consensus (Zwischenberger & Jacobe, 2011). Therefore, the present case adds further practical evidence regarding the potential benefits of physiotherapy management in patients with linear scleroderma.

In our case, the greatest therapeutic effect appeared to result from emphasis on myofascial release and gentler manual techniques. Clinically, a reduction in tissue induration, improved elasticity and mobility of soft tissues, and decreased visible irregularities of the skin and subcutaneous tissue were observed. Such a response may be explained by the effects of manual techniques on fascial gliding, local circulation, reduction of muscle tension, and improvement of proprioceptive perception. Although the precise mechanisms in patients with scleroderma have not yet been sufficiently investigated, the findings suggest that fascia-oriented approaches may be clinically relevant, particularly in patients with pronounced soft tissue fibrosis.

An important finding of this case was that the patient did not tolerate more intensive techniques well, as these occasionally triggered an adverse or protective tissue response. In contrast, more gradual and less aggressive methods were more effective and better tolerated. This is a clinically relevant message for physiotherapists, as excessive mechanical aggressiveness is probably not appropriate when treating fibrotic and chronically altered tissues. Instead, gradual modulation of load combined with continuous monitoring of the patient's response appears to be preferable. Individualization of therapy is therefore essential.

In addition to passive techniques, the active component of rehabilitation likely also played an important role. Exercises aimed at strengthening the gluteal musculature, the transversus abdominis muscle, and improving pelvic control most likely contributed to reduced gait asymmetry and better movement control. In patients with long-standing compensatory patterns, treatment of soft tissues alone is often insufficient unless accompanied by movement re-education and stabilization training. In this case, the combination of manual techniques and therapeutic exercise proved to be a rational and functionally effective approach.

It is important to emphasize that this is a single case report; therefore, the findings cannot be directly generalized to the wider patient population. In addition, objective outcome measures (e.g., goniometry, LoSCAT, validated functional questionnaires, or quality-of-life instruments) were not systematically applied. Consequently, the assessment of progress was based mainly on clinical observation, palpation, functional assessment, and

the patient's subjective report. Nevertheless, the observed changes were sufficiently pronounced and multidimensional to provide important clinical value.

Future prospective studies with larger patient samples, standardized outcome measures, and comparisons of different physiotherapy approaches are needed. It would be particularly valuable to investigate the effects of myofascial techniques, manual therapy, and targeted therapeutic exercise in patients with linear scleroderma affecting the lower limbs. Our case suggests that physiotherapy may represent an important and safe component of comprehensive management and may significantly contribute to improving patients' functional status (Fett & Werth, 2011; Kreuter et al., 2016).

6. Conclusions

The presented case shows that individually tailored physiotherapy management can significantly contribute to improving functional status in patients with juvenile linear scleroderma of the lower limb. After five months of regular treatment, improvements were observed in range of motion, reduction of compensatory movement patterns, better gait symmetry, and improved soft tissue quality. The patient also reported better subjective well-being and easier performance of daily and sports activities. In the presented case, a combination of myofascial release, gentle manual techniques, targeted therapeutic exercise, and individually adjusted progression of loading proved to be particularly beneficial. The findings suggest that in patients with soft tissue fibrosis and long-standing movement limitations, it is important to select gradual, well-tolerated therapeutic approaches and combine them with active exercise aimed at improving stability and functional movement. Although this is a single case report, the findings support the inclusion of physiotherapy as an important component of multidisciplinary management in patients with localized or linear scleroderma. Further studies involving larger patient samples and standardized outcome measures will be needed to more precisely define the most effective physiotherapy approaches.

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Conflicts of Interest: The authors declare no conflict of interest.

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Research

Membrane Biophysics-Based Mechanisms of Cancer Progression: the Active Decoupling / Vanguard Hypothesis

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Abstract:

Accumulating evidence indicates that the complex intra and intercellular infrastructure composed of membranous nanostructures—including tunneling nanotubes (TNTs), and extracellular nanoparticles (EPs) — serve as a critical physical determinant of cancer progression, metabolic rewiring, and therapy potential. Further, we hypothesize that the biogenesis and stability of these communication conduits are intrinsically linked with local membrane composition and physical properties. Pathological alterations in lipid and protein shape, and therefrom induced changes in membrane free energy may favour spontaneous membrane budding and subsequent tubule elongation or shedding extracellular vesicles (EVs). Because malignant nanostructures depend on these permissive physical landscapes, we propose that disrupting this physical network represents a viable oncology frontier. Specifically, therapeutic manipulation of the host membrane composition via externally added membrane curvature-modulating compounds, amphiphilic molecules, or membrane-active agents, can alter membrane properties and destabilize and collapse the tumor's intra and intercellular infrastructure, presenting a novel, mutation-independent strategy to halt cancer invasion.

Keywords: Cancer; Cellular infrastructure; Tunneling nanotubes; Extracellular vesicles; Extracelular particles; Cancer theranostics

1. Introduction

Early description of breast cancer was recorded already on ancient Egyptian medical texts cca 2500 BC (Hajdu, 2016). It concluded that the disease had no treatment. Since then, considerable progress has been made, and lifetime cured cases are registered (Wagle et al., 2025). However, the underlying mechanisms are not yet completely understood. As tumors are composed of cells, it is necessary to study the features at the cellular and subcellular levels. Extensive study has been devoted to genetic mechanisms of cancer progression, but recently, highly curved membranous nanostructures have also become a subject of increasing interest. Membranes are not just passive bags; they are active, mechanosensitive physical landscapes. Tunneling nanotubes and extracellular particles are involved in intercellular communication and are potentially important players in cancer progression (Kralj-Iglič et al., 2012). We argue that cancer progression is fundamentally driven by biophysical alterations of cellular membranes, in particular, of membranous nanostructures that serve as vectors for metabolic, structural and signaling advantages.

2. Tunneling nanotubes as the cell infrastructure

A landmark experimental research (Iglič et al., 2003) provided direct evidence of phospholipid nanotubes acting as platforms for the traveling of localized vehicles to ferry enclosed solutions between different membrane-enclosed compartments (**Figure 1A**). The gathered experimental evidence indicated that these nanoconduits are present in archaea, bacteria, plants, and mammals (Gozen and Dommersnes, 2020). While the intercellular communication by tunneling nanotubes has been acknowledged (Rustom et al., 2004; Veranič et al., 2008), it was hypothesized that membranous structures, in particular the nanotubes, are also present inside the cells where they may direct the transport of material between the compartments (Iglič et al., 2003).

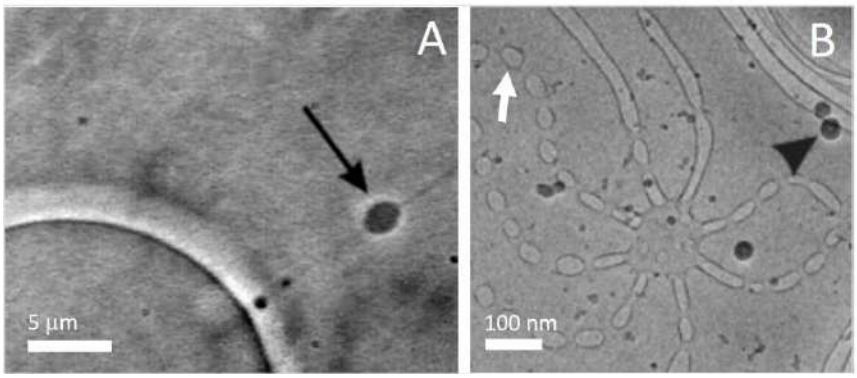

Figure 1A: Phase contrast optical microscope image of directed transport along the phospholipid nanotube by a gondola (black arrow). From (Iglič et al., 2003), with permission; **B:** Cryogenic electron microscope image of tubular to globular (white arrow) shape transition in phospholipid membrane. Black triangle points to an electron-dense particle. From (Spasovski et al., 2024, CC BY-NC 4.0 license). Under a phase contrast microscope, optical diffraction effects and phase halos artificially broaden the visual silhouette of the tube, making it appear significantly thicker in the image than it is in physical reality.

3. Deviatoric elasticity – a hallmark of stability of the membranous nanostructure shape

To mathematically and physically explain how a cell can maintain a directed nanotube infrastructure instead of breaking down into random, wandering spherical vesicles, we must look at deviatoric elasticity (also frequently referred to in membrane biophysics as the anisotropic bending elasticity or the spontaneous curvature anisotropy of lipid bilayers) (Kralj-Iglič et al., 2020). Standard membrane theories (like the Helfrich spontaneous curvature model) treat the lipid bilayer as an isotropic, fluid sheet (Helfrich, 1973). However, real biological membranes are packed with anisotropic components—such as elongated proteins, asymmetric lipids, and oriented cytoskeletal attachments. Deviatoric elasticity accounts for the physical reality that these molecules bend differently in one direction than they do in another and can – as they are free to rotate – undergo

orientational ordering. This represents another degree of freedom of the system and can lower the free energy of the membrane. On the spherical parts, there is no orientational ordering of the membrane constituents as all directions are equivalent. On the tubular parts, however, orientational ordering lowers the membrane free energy, depending on the tube diameter, and if the membrane contains anisotropic constituents with the diameter of the tube small enough, prefer the tubular shape over the globular one (Kralj-Iglič et al., 2002; Kralj-Iglič et al., 2020).

4. In tumour, cell size and integrity are intricately linked

In some malignancies, the cells are much smaller than a typical healthy cell of that tissue type (Shashni et al. 2018, Jiang et al., 2017). In a normal cell, the nucleus is small and takes up a minor fraction of the total cell volume. Even if a cancer cell shrinks to a small overall size, its nucleus remains large, resulting in a high nucleus-to-cytoplasm ratio—one of the most reliable visual triggers a pathologist uses to diagnose cancer.

One of possible reasons for small amount of cytoplasm could be that the cell is shrinking because it is actively casting off material. Cancer cells undergo constant membrane fragmentation preceded by budding. The cancer cell pushes out a piece of its plasma membrane, packs it with materials, and pinches it off (Zhu et al., 2021). If an aggressive cancer cell continuously pinches off thousands of microvesicles (ranging from 100 nm to large oncosomes up to 1 μm, it is constantly bleeding out its own plasma membrane and cytoplasm (Guzowska et al., 2026). Unless it can regenerate its cytoplasm at the exact same rate, the cell will physically shrink. This leaves behind a stripped-down, streamlined cell with a disproportionately large nucleus. If a malignant cell excessively sheds extracellular particles, its total cytoplasmic volume decreases over time, leaving a physically smaller mother cell with a relatively large nucleus.

The high nucleus-to-cytoplasm ratio characteristic of highly metastatic cancer cells may not be merely a consequence of rapid cell division, but an active manifestation of hyper-vesiculation. Malignant cells reduce their cytoplasmic volume by aggressively shedding extracellular vesicles and large oncosomes; this mass extrusion simultaneously de-bulks the parent cell for streamlined amoeboid migration while biochemical weaponizing the local and distant microenvironments to drive efficient metastasis.

If a cell has a small amount of cytoplasm because it has aggressively shed its mass into the environment, that cell is statistically much more dangerous and metastatic. The fragments it leaves behind serve as a vanguard force for tumor spread. The cytoplasm lost by the cancer cell is often packed with immunosuppressive proteins and signaling RNAs. As these fragments drift away, they exhaust and paralyze local T-cells and natural killer cells, creating a safe zone for the tumor (Lucotti et al., 2022). The shed particles travel through the bloodstream ahead of the cancer cell. They land in distant organs (like the lungs or liver) and forcefully reprogram the local tissue to make it welcoming for when the shrunken parent cell eventually arrives.

5. Destruction of the tumor from within

When a solid tumor grows past a certain diameter (typically around 2 to 4 millimeters), it outstrips its local blood vessel supply (Lee et al., 2018). Cells at the leading edge are often physically smaller in cytoplasmic volume than healthy epithelial cells, retaining a highly prominent, large nucleus. They are small because they are metabolically hyperactive. They actively shed their cytoplasm in the form of extracellular vesicles and large oncosomes forward into the healthy tissue (Deisboeck et al., 2006). They consume all the incoming oxygen and glucose, leaving the cells deep in the center to starve in a state of severe hypoxia (oxygen deprivation). On the border of the necrotic core, cancer cells avoid death by using autophagy to shrink their cytoplasmic volume, while actively fragmenting off microvesicles. In the starved center, without oxygen and glucose, they cannot generate ATP. Their membrane pumps fail, causing water to rush into the cells. These starving cells swell up to a much larger, unstable size. Because the cell continues to expand without metabolic control, the outer membrane loses all structural integrity, and ruptures. Unregulated, catastrophic fragmentation of cancer cells takes over via a specific form of cell death. The cell fragments into unstructured debris, spilling its raw contents directly into the tissue and releasing pro-inflammatory cellular debris that triggers tumor-promoting inflammation (Lee et al., 2018).

6. Integrity of tissue

In healthy epithelial tissues, E-cadherins (Epithelial Cadherins) are transmembrane glycoproteins that serve as the primary molecular adhesive holding cells together (Li et al., 2012). They act as a structural anchor that establishes tissue architecture, maintains cell polarity, and regulates intercellular communication. In solid tumors (particularly carcinomas), the down-regulation, loss, or functional inactivation of E-cadherins is a definitive hallmark of progression (Baskar Vimala et al., 2025). From a purely physical perspective, uncoupling E-cadherins from the cortical actin cytoskeleton removes the structural tension that keeps the cell membrane flat and stable. The bending rigidity of the lipid bilayer drops significantly. The internal actomyosin contractile machinery becomes unconstrained, causing the unanchored plasma membrane to undergo continuous, localized budding. This mechanical instability increases the frequency of membrane fission events, causing the cell to shed massive quantities of EPs into its surroundings. Without E-cadherins to hold them back, cells at the tumor surface can break away. They don't always detach as single cells; instead, they often break off in multicellular fragments or clusters (Circulating Tumor Cell clusters). These fragmented clusters are highly lethal. Because the cells inside the cluster still retain some internal cell-to-cell contact, they protect each other from dying in the bloodstream, possessing up to 100 times higher metastatic potential than single wandering cancer cells. The loss of E-cadherin does not just let the cell float away; it triggers an internal biochemical chain reaction that directly accelerates the micro-fragmentation (shedding) of the cytoplasm. Normally, the tail end of E-cadherin binds to a signaling protein called beta-catenin inside the cell. When E-cadherin disappears, beta-catenin is liberated and rushes into the cell's nucleus, turning on genes that completely dismantle the rigid, organized cytoskeleton (Gloerich et al., 2017). Without the structural framework of E-cadherins maintaining a flat, stable cell shape, the plasma membrane becomes highly unstable and fluid. The internal contractile forces (driven by the RhoA/ROCK pathway) are unleashed. The cell begins to violently bubble and bleb, shifting its metabolism into overdrive to pump out extracellular vesicles and large oncosomes (Gaptulbarova et al., 2024). The cell loses its wide, flat epithelial shape because E-cadherins are no longer stretching it against its neighbors. It balls up into a smaller, rounded, fluid shape (Alhalhooly et al., 2021). As it rolls or crawls away, the unstable, unanchored membrane allows it to rapidly shed its vanguard vesicles forward into the tissue. The cell physically deflates its cytoplasmic volume while keeping its large, genetically packed nucleus intact.

7. The Active Decoupling / Vanguard hypothesis

We hypothesize that in normal homeostasis, intracellular and intercellular transport is directed and energetically passive, occurring via localized dilatations moving along a continuous infrastructure of phospholipid nanotubes driven by membrane tension gradients (**Figure 1A**). In malignancy, this structural infrastructure becomes highly defective due to the cytoskeletal uncoupling associated with E-cadherin loss. Unable to maintain internal directed transport, the cell undergoes localized membrane accumulation, forcing a transition from internal dilatation-mediated routing to chronic, external membrane budding and fission. This infrastructural collapse drives the net loss of cytoplasmic volume, generating the characteristic high nucleus-to-cytoplasm ratio while generating the vanguard extracellular particles.

The membrane contains elongated, anisotropic proteins (such as BAR-domain proteins, oriented tubulin/actin complexes, or asymmetric membrane-spanning inclusions). These molecules have a distinct preference for in-plane orientation in the membrane. They better fit into a cylinder than into a globule, but are physically strained due to geometrical constraints. When these anisotropic components align themselves along the circumference of a nanotube, the system hits a state of low membrane free energy. The orientation of the molecules perfectly matches the highly asymmetric physical shape of the cylinder. If a thermal fluctuation or an external force attempts to pinch that nanotube down into a series of detached, round globular vesicles would inflict a massive deviatoric energy penalty. As long as the deviatoric bending modulus is sufficiently high, this energy barrier physically locks the membrane into its cylindrical nanotube state. It structurally forbids the fission process that would otherwise slice the nanotube into a chaotic cloud of wandering vesicles.

The normal cell synthesizes and perfectly organizes the anisotropic, membrane-shaping proteins (and their cytoskeletal anchors, heavily regulated by E-cadherin signaling). This generates a high deviatoric bending modulus, mechanically stabilizing a continuous, robust internal nanotube highway capable of directed cargo trafficking via localized dilatations – gondolas (**Figure 1A**). Because of this energy barrier, the network cannot easily degrade into globular vesicles, ensuring directed, energy-free transport along the continuous infrastructure. In cancer cells, the infrastructure becomes defective. The loss of E-cadherins and the resulting cytoskeletal disassembly disorganizes or downregulates these specialized anisotropic molecules. The deviatoric stabilization collapses. Lacking this directional elastic protection, the membrane loses its cylindrical stability and spontaneously breaks down into isotropic, globular vesicles via unchecked budding and fission, driving the mass-shedding state of the Vanguard Hypothesis (**Figure 1B**).

8. Therapeutic implications based on the Active Decoupling / Vanguard Hypothesis

Because membrane self-assembly is fundamentally reversible, therapeutic strategies aimed at restoring E-cadherin expression or stabilizing the cortical actin skeleton could theoretically re-establish the critical force thresholds and deviatoric elasticity required to rebuild the cell's internal nanotubular infrastructure. Artificially forcing the restoration of this continuous directed transport network would effectively reverse the mass-transport imbalance, halting the hyper-vesiculation of vanguard particles and freezing the cell's metastatic capacity. This concept opens up a profound new angle for therapeutic prophylaxis. If the destruction of the infrastructure is what drives metastasis, then cancer therapy should focus on stabilizing the nanotubular network.

9. Conclusions

In practice, repairing a defective nanotubular infrastructure can be achieved through a multi-modal biophysical intervention. Combining small-molecule epigenetic agents (to restore the E-cadherin/β-catenin actin anchors) with intravenously delivered BAR-domain biomimetic nanoparticles could restore both the pulling mechanics and the anisotropic deviatoric elasticity required to stabilize cylinders. When coupled with acoustic microenvironmental tuning to optimize lateral membrane tension, this combined approach physically suppresses the transition from continuous internal transport to irreversible external fission. This effectively freezes the mass-transport imbalance driving the Vanguard Hypothesis and stops metastasis at a purely mechanical level.

Conflicts of Interest: The author declares no conflict of interest.

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Research

Correlation of Knee Joint Stabilization Force with Anterior and Mediolateral Rotational Laxity Using the Arthrometer

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Abstract:
Knee joint laxity is commonly evaluated using instrumented arthrometers; however, the relationship between externally applied stabilization force and measured anterior and rotational laxity remains insufficiently explored. This study aimed to examine the correlation between knee joint stabilization force and both anterior and mediolateral rotational knee laxity in healthy adults. Methods: A cross-sectional study was conducted on 100 healthy participants (50 males and 50 females; aged 18–29 years). One randomly selected knee per participant was assessed using the DYNEELAX arthrometer. Anterior knee laxity was measured at loading forces of 134 N, 150 N, and 200 N. Mediolateral rotational laxity was assessed during medial and lateral rotation at torques of 3 Nm and 5 Nm. Stabilization force was recorded during standardized limb fixation. Associations were analysed using Spearman's correlation coefficient r_s. No meaningful correlations were observed between stabilization force and anterior knee laxity at any loading condition (r_s = -0.055 to -0.061). In contrast, moderate, statistically significant negative correlations were identified between stabilization force and mediolateral rotational laxity across all tested conditions (medial 3 Nm: r_s = -0.455; medial 5 Nm: r_s = -0.554; lateral 3 Nm: r_s = -0.554; lateral 5 Nm: r_s = -0.553; all $p < 0.001$). Conclusion: Stabilization force shows no meaningful correlation with anterior knee laxity but demonstrates a moderate inverse correlation with mediolateral rotational laxity. These findings indicate that rotational laxity is more sensitive to testing conditions, emphasizing the importance of standardized stabilization procedures in instrumented knee joint assessment.

Keywords: Knee biomechanics; Ligamentous stability; Tibiofemoral kinematics; Stabilization force; Stability; Healthy adults

1. Introduction

The knee joint, consisting of the tibiofemoral and patellofemoral articulations, is a complex and dynamic structure responsible for load transmission and mobility during activities of daily living (Paterno & Hewett, 2008). It allows a wide range of motion, primarily in flexion–extension and axial rotation, while maintaining joint stability under substantial mechanical demands (Hirschmann & Müller, 2015).

Biomechanically, the knee is classified as a modified hinge joint (trochoginglymus), where motion results from a coordinated interaction of rolling, gliding, and rotational movements. Its kinematics are described by six degrees of freedom. These include rotational components (flexion–extension, internal–external rotation, varus–valgus) and translational components (anterior–posterior, medial–lateral, compression, and distraction). These components interact to maintain joint stability while allowing physiological motion (Hirschmann & Müller, 2015; Noyes et al., 1991).

Knee joint motion differs between open and closed kinetic chain conditions. In open kinetic chain movements, flexion is characterized by posterior rolling and gliding of the tibial plateaus relative to the femoral condyles, accompanied by medial rotation of the tibia, particularly during the initial phase of flexion (approximately the first 30°). During extension, the tibia translates anteriorly through a combination of rolling and gliding, with the terminal phase (last 30°) associated with lateral rotation. In contrast, in closed kinetic chain movements, the kinematic pattern is reversed. Extension involves anterior rolling and posterior gliding of the femoral condyles on the tibial plateaus, together with medial rotation of the femur in the final degrees of motion, commonly referred to as the "screw-home" mechanism. During flexion, posterior rolling and anterior gliding of the femoral condyles occur, accompanied by lateral rotation of the femur at the onset of movement (McGinty et al., 2000).

Joint laxity is an inherent characteristic of physiological joint motion and is assessed passively in clinical settings (Schmitt et al., 2008). Anterior knee laxity is defined as the anterior displacement of the tibia relative to the femur (Shultz et al., 2009), whereas mediolateral rotational laxity refers to the rotational movement of the tibia in relation to the femur (Vassalou et al., 2016).

Increased knee laxity has been associated with a higher risk of ligamentous injury, particularly involving the anterior cruciate ligament (Myer et al., 2008; Pasanen et al., 2025), as well as other knee ligaments (Kim et al., 2010). Quantitative analyses indicate that each additional millimetre of anterior knee laxity increases the likelihood of traumatic knee injury by approximately 30% (odds ratio 1.3) (Vauhnik et al., 2008). Moreover, elevated joint laxity has been linked to the development of osteoarthritis (Heidari, 2011), and individuals with excessive physiological laxity have been shown to exhibit movement patterns associated with non-contact anterior cruciate ligament injury mechanisms (Mouton et al., 2016). Given these associations, assessment of knee laxity plays an important role in clinical diagnosis, rehabilitation, and injury prevention screening. Traditionally, anterior and rotational laxity are evaluated using manual clinical tests, including the Lachman test, anterior drawer test, dial test, and pivot-shift test (Mouton et al., 2016). However, these assessments are limited by their dependence on examiner experience and their inability to provide precise and reproducible quantitative measurements (Seil et al., 2017).

To address these limitations, several instrumented devices have been developed to standardize the evaluation of knee laxity and replicate manual testing procedures under controlled conditions (Mouton et al., 2016). Commonly reported devices include the KT-1000, KT-2000, GNRB, Rolimeter, and Telos systems (Magdič et al., 2023). More recently, the DYNEELAX® arthrometer has been introduced, enabling sequential assessment of sagittal and axial laxity within a single device without repositioning the tested limb (Mihalinec et al., 2024).

Beyond enabling standardized quantification, instrumented measurements also allow controlled application of stabilization forces during testing. The magnitude of posteriorly directed stabilization force applied at the patella and ankle has been shown to influence measured knee laxity values (Nascimento et al., 2024). Although stabilization force has been suggested to influence measured knee laxity, its direct relationship with anterior and rotational laxity has not yet been specifically examined. Therefore, the purpose of this study was to investigate the relationship between knee joint stabilization force and both

anterior and mediolateral rotational laxity, as assessed using the DYNEELAX® arthrometer.

2. Material and Methods

2.1. Ethical approval and study setting

Ethical approval was obtained from the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-436/2024-2711-3). Institutional permission was granted by the Faculty of Health Sciences, University of Ljubljana. All participants provided written informed consent before participation and were informed about the study aims and procedures both verbally and in writing.

The study was conducted at the Biomechanics Laboratory, Faculty of Health Sciences, University of Ljubljana, between June and September 2025. All measurements were performed by a physiotherapist newly trained in the use of the DYNEELAX® arthrometer, who completed a structured training program before data collection. Measurement reliability was confirmed in a pilot study demonstrating acceptable reliability.

2.2. Study design

A cross-sectional study design was used. A total of 100 healthy adults were included (50 males and 50 females). One randomly selected knee from each participant was assessed once. Demographic and anthropometric data were collected, including age, sex, lower limb dominance, body height, and body mass, from which body mass index (BMI) was calculated. In female participants, additional data were collected regarding menstrual cycle regularity, oral contraceptive use, and premenstrual symptoms, due to the potential influence of sex hormones on ligament laxity (Shultz et al., 2004). Lower limb dominance was determined using a standardized question ("If you were to kick a ball toward a target, which leg would you use?") and verified with a practical ball-kicking task. In cases of inconsistency, the assessment was repeated (van Melick et al., 2017).

2.3. Participants

Participants were recruited using a convenience sampling approach through social media and personal invitations. Eligibility criteria included being 18–30 years old, having no history of lower limb injury or disease, no prior lower extremity surgery, not participating in other studies on the day of testing, and being in good general health. Exclusion criteria were current or previous lower limb pain, history of injury, disease, or surgery affecting the lower extremities, neurological or systemic musculoskeletal conditions, BMI greater than 35 kg/m², pregnancy, and inability to follow instructions or comply with the protocol.

2.4. Measurement instrument

The DYNEELAX® arthrometer is an automated device used to quantify knee joint laxity by measuring anterior–posterior tibial translation and mediolateral tibial rotation. It applies controlled translational and rotational loads to the tibia and records the mechanical response of structures (Genourob, n.d.).

Anterior tibial translation is assessed using forces ranging from 0 to 300 N, applied to the proximal posterior tibia. Displacement is recorded with a sensor placed over the tibial tuberosity, with a resolution of 0.1 mm, enabling quantification of laxity (mm/N). Results are presented as force–displacement curves, where the slope reflects ligament stiffness (Genourob, n.d.; Guegan et al., 2024). Rotational laxity is assessed using torques between 1 and 10 N·m. Tibial rotation is recorded in degrees (°) with a precision of 0.1°, and results are presented as torque–angle curves.

Previous studies have reported moderate reliability for anterior laxity (ICC 0.578–0.71 inter-rater; 0.631–0.71 intra-rater) and good to excellent reliability for rotational laxity (ICC 0.822–0.94 inter-rater; 0.916–0.94 intra-rater) (Mihalinec et al., 2024). Excellent intra-rater reliability for anterior laxity has also been reported in healthy adults (ICC 0.91–0.96) (Nascimento et al., 2024).

The testing protocol followed previously published procedures and manufacturer guidelines.

2.5. Testing protocol

Participants were instructed to avoid high-intensity activities involving rapid directional changes on the day of testing. They received standardized instructions and were encouraged to remain relaxed throughout the procedure. Participants lay in a supine position on a customized examination table, with the trunk flexed to approximately 30°. The tested limb was positioned at 20° of knee flexion and neutral rotation using an adjustable support

aligned with the knee joint line. The lower limb was secured using standardized strapping, applied from distal to proximal. Strap tension ranged from 80 to 150 N and was adjusted to participant tolerance. For anterior translation, the sensor was placed over the tibial tuberosity perpendicular to the skin. For rotational measurements, the sensor was positioned on the anterior tibia approximately 2 cm distal to the translation plate. Calibration was performed according to manufacturer guidelines. Anterior laxity was assessed first, followed by rotational laxity. The anterior protocol included one trial at 134 N, one at 150 N, and three trials at 200 N. Rotational testing included one trial at 3 N·m and three trials at 5 N·m for both medial and lateral rotation. The total testing time was approximately 20 minutes.

2.6. Statistical analysis

Data were exported and checked for accuracy before analysis. Statistical analyses were performed using jamovi (version 2.7.12) and Microsoft Excel. Normality was assessed with the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median and interquartile range. Categorical variables are expressed as percentages. For anterior knee laxity assessment, values obtained at 134 N, 150 N, and the final repetition at 200 N were analysed, while for mediolateral rotational laxity, values obtained at 3 N·m and the final repetition at 5 N·m were analysed.

Between-group comparisons were performed using the Mann–Whitney U test or independent samples t-test, as appropriate. The Wilcoxon signed-rank test was used for repeated measures. Categorical variables were analysed using the chi-square or Fisher's exact test. Associations between anterior and rotational laxity were assessed using Spearman's correlation coefficient r_s. Correlation strength was interpreted as negligible (0.00–0.09), weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89), or very strong (0.90–1.00) (Schober et al., 2018). Statistical significance was set at $\alpha = 0.05$.

3. Results

3.1. Participant characteristics

The study included 100 healthy adult participants, 50 males and 50 females, aged 18–29 years. In both sexes, 25 left and 25 right knee joints were assessed. Age and body height were not normally distributed (p-values < 0.001 and 0.026). Body mass and body mass index were normally distributed (p-values 0.082 and 0.144). Within each sex, there were no statistically significant differences between participants whose left or right knee joint was assessed (p-values between 0.437 and 1).

Anthropometric data and other participant characteristics are presented in **Table 1**.

3.2. Correlation of knee joint stabilization force with anterior laxity

Table 2 presents descriptive statistics for knee joint stabilization force and anterior knee laxity measured at 134 N, 150 N, and 200 N. The mean stabilization force was 135.33 N (median 137 N; IQR 13 N). Mean anterior laxity values were 2.92 mm at 134 N, 3.21 mm at 150 N, and 4.52 mm at 200 N, with corresponding medians of 2.85 mm, 3.05 mm, and 4.28 mm. The observed ranges increased with higher loading levels, with maximum values of 6.22 mm, 6.63 mm, and 8.11 mm at 134 N, 150 N, and 200 N, respectively. All variables deviated significantly from normal distribution (Shapiro–Wilk, $p \leq 0.001$)

Figures 1–3 present scatter plots showing the relationship between knee joint stabilization force and anterior laxity at 134 N, 150 N, and 200 N. Spearman's correlation coefficients (r_s) between knee joint stabilization force and anterior laxity were negative under all three loading conditions (134 N: $r_s = -0.055$; 150 N: $r_s = -0.061$; 200 N: $r_s = -0.058$).

Table 1. Anthropometric data of participants by sex and side of the assessed knee joint.

	Men			Women			
	n = 50			n = 50			
	Left	Right		Left	Right		All
Number	25	25	/	25	25	/	100
(%)	(25)	(25)		(25)	(25)		(100)
Age (years)							
Me	22	22	†p = 0.505	22	21	†p = 0.708	22
IQR	3	3		3	2.75		3
Body height (cm)							
Me	180	180	†p = 0.915	166	167	†p = 0.437	175
IQR	11	13		7	7		15
Body mass (kg)							
$\bar{x}$	25	25	*p = 0.480	23	23	*p = 0.810	24
SD	2	2		3	3		3
Dominant leg – n (%)	4	6		2	2		14
Left – n (%)	(16)	(24)		(8)	(8)		(14)
Dominant leg	21	19	‡p = 0.480	23	23	§p = 1	
Right – n (%)	(84)	(76)		(92)	(92)		(86)
RMC - n				19	21	/	40
(%)				(76)	(8)		(12)
O.C. - n	/	/	/	4	2	/	6
(%)				(16)	(8)		(12)
PMS - n	/	/	/	4	5	/	9
(%)				(16)	(20)		(18)

BMI = body mass index; IQR = interquartile range; Me = median; O. C. = oral contraceptives; PMS = premenstrual symptoms; p = p-value; RMC = regular menstrual cycle; SD = standard deviation; $\bar{x}$ = mean; * = independent samples t-test (comparison between left and right side within the same sex); † = Mann–Whitney U test (comparison between left and right side within the same sex); ‡ = χ^2 test (comparison of distribution between left and right side and lower limb dominance in males); § = Fisher's exact test (comparison of distribution between left and right side and lower limb dominance in females)

Table 2. Descriptive statistics of knee joint stabilization force and anterior knee laxity measured at 134 N, 150 N, and 200 N.

	Force (N)	134 N (mm)	150 N (mm)	200 N (mm)
Mean	135	2.92	3.21	4.52
Median	137	2.85	3.05	4.28
IQR	13	1.06	1.19	1.22
Minimum	103	1.41	1.59	2.83
Maximum	149	6.22	6.63	8.11
Shapiro-Wilk p	< 0.001	0.001	<0.001	<0.001

IQR = interquartile range

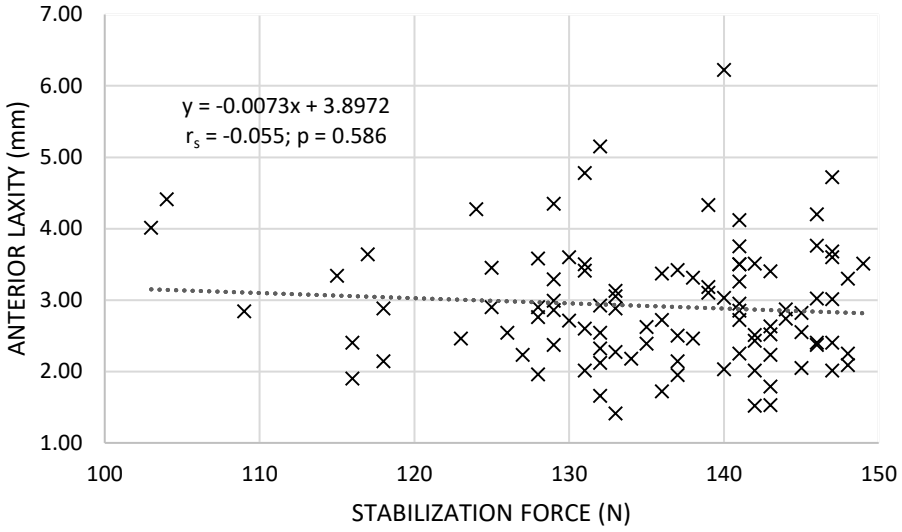

Figure 1. Correlation of knee joint stabilization force with anterior laxity at 134 N. The dotted line represents the fitted regression line; the corresponding equation, r_s, and p-value are shown within the figure.

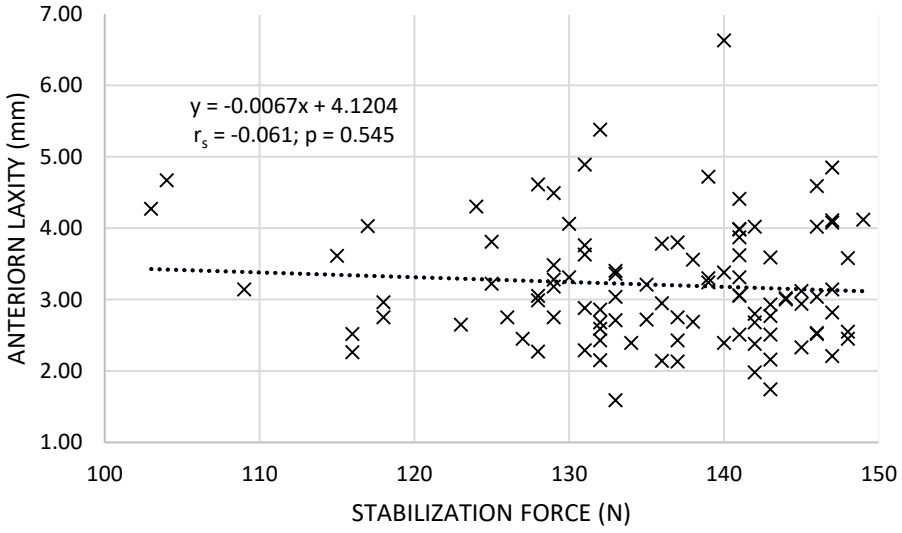

Figure 2. Correlation of knee joint stabilization force with anterior laxity at 150 N. The dotted line represents the fitted regression line; the corresponding equation, r_s, and p-value are shown within the figure.

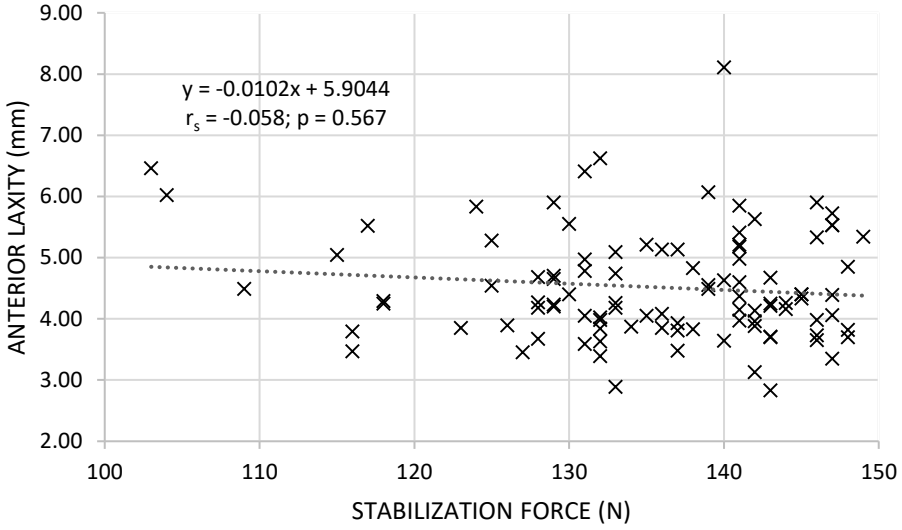

Figure 3. Correlation of knee joint stabilization force with anterior laxity at 200 N. The dotted line represents the fitted regression line; the corresponding equation, r_s, and p-value are shown within the figure.

3.3. Correlation of knee joint stabilization force with mediolateral rotational laxity

Table 3 presents descriptive statistics for knee joint stabilization force and mediolateral rotational knee laxity measured during medial and lateral rotation at 3 Nm and 5 Nm. Median medial rotation laxity was 4.67° at 3 Nm and 7.65° at 5 Nm, while median lateral rotation laxity was 6.22° at 3 Nm and 10.44° at 5 Nm. The interquartile ranges increased with higher torque levels, with the greatest variability observed for lateral rotation at 5 Nm (IQR 9.33°). Maximum values were 12.37°, 19.61°, 16.17°, and 25.83° for medial 3 Nm, medial 5 Nm, lateral 3 Nm, and lateral 5 Nm, respectively. Shapiro–Wilk test results showed that all variables significantly deviated from normal distribution ($p \leq 0.05$).

Table 3. Descriptive statistics of knee joint stabilization force and mediolateral rotation knee laxity measured at 3 and 5 Nm.

	Medial rotation (Nm)	Medial rotation (Nm)	Lateral rotation (Nm)	Lateral rotation (Nm)
	3 Nm	5 Nm	3 Nm	5 Nm
Median	4.67	7.65	6.22	10.44
IQR	3.42	5.82	6.54	9.33
Minimum	0.24	2.6	1.18	2.97
Maximum	12.37	19.61	16.17	25.83
Shapiro-Wilk p	0.026	<0.001	<0.001	<0.001

IQR = interquartile range

Figures 4 and 5 present scatter plots showing the relationship between knee joint stabilization force and mediolateral rotational laxity at 3 and 5 N·m. Spearman's correlation coefficients between knee joint stabilization force and rotational laxity were negative under all conditions (medial 3 Nm: r_s = -0.455; medial 5 Nm: r_s = -0.554; lateral 3 Nm: r_s = -0.554; lateral 5 Nm: r_s = -0.553), and all correlations were statistically significant ($p < 0.001$).

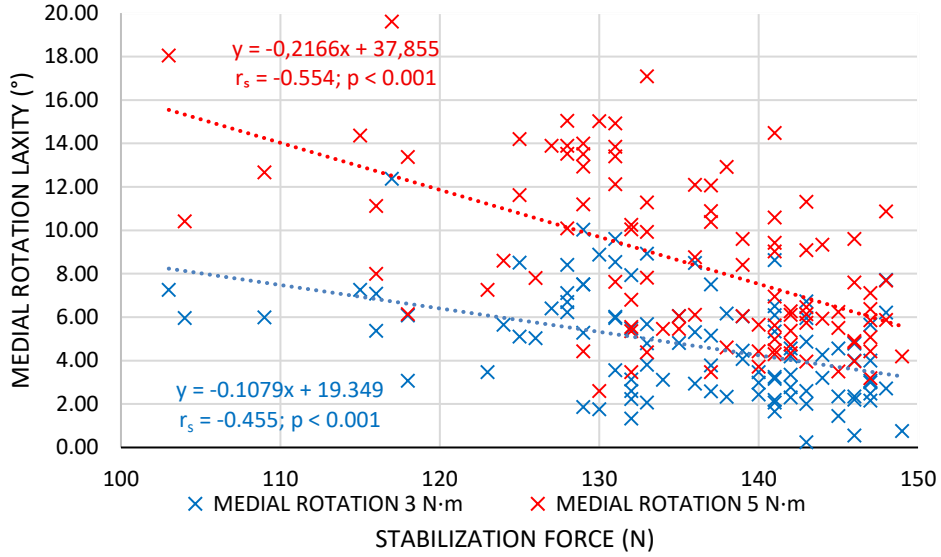

Figure 4. Correlation of knee joint stabilization force with medial rotation laxity at 3 and 5 Nm. The dotted line represents the fitted regression line; the corresponding equation, r_s, and p-value are shown within the figure.

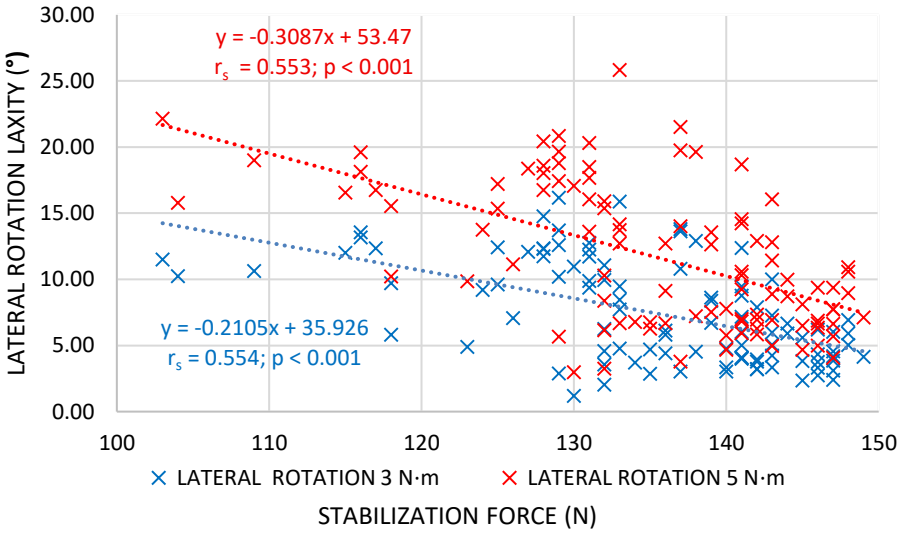

Figure 5. Correlation of knee joint stabilization force with lateral rotation laxity at 3 and 5 Nm. The dotted line represents the fitted regression line; the corresponding equation, r_s, and p-value are shown within the figure.

4. Discussion

The aim of this study was to investigate the relationship between knee joint stabilization force and both anterior and mediolateral rotational knee laxity in healthy young adults using the DYNEELAX® arthrometer. The principal finding was that stabilization force showed no meaningful relationship with anterior knee laxity, while moderate, statistically significant negative correlations were observed with mediolateral rotational laxity. These findings suggest that the influence of stabilization during instrumented knee testing differs depending on the type of laxity being assessed.

The absence of a significant association between stabilization force and anterior laxity across all three loading conditions (134 N, 150 N, and 200 N) indicates that anterior laxity measurements may be relatively robust to variations in external fixation force within the tested range. Although weak negative correlations were observed, their magnitude was negligible, suggesting that increased stabilization does not substantially alter anterior translation values in healthy knees. This may be explained by the biomechanical characteristics of sagittal plane knee stability. At approximately 20° of knee flexion, as used in the present protocol, anterior tibial displacement is primarily restrained by the anterior

cruciate ligament (Kreder & Hawker, 2010), with additional support from secondary passive stabilizers such as the iliotibial band, collateral ligaments, menisci, and surrounding capsuloligamentous structures (Rahnemai-Azar et al., 2017). Therefore, suggesting that anterior laxity measurements primarily reflect intrinsic ligamentous behaviour, with minimal influence of externally applied stabilization force within the tested range.

This finding is consistent with previous work using the DYNEELAX® system, which reported high intra-rater reliability for anterior translation under standardized stabilization conditions, indicating that anterior measurements are relatively stable, reliable and reproducible (Cojean et al., 2023). The present results build on these observations by suggesting that even when stabilization force varies between participants, anterior laxity values remain largely unaffected.

In contrast, the results showed moderate negative correlations between stabilization force and rotational laxity under all tested torque conditions. The strongest association was observed for medial rotation at 5 N·m (r_s = -0.554), with similar values for lateral rotation. These findings indicate that greater stabilization force is associated with lower measured rotational displacement. From a biomechanical perspective, this result is plausible, as greater stabilization likely increases patellofemoral joint compression and enhances joint stability, thereby limiting mediolateral rotational freedom (Cojean et al., 2023).

Rotational knee laxity is known to be more sensitive to testing conditions (Mouton et al., 2016), as axial rotation is influenced not only by intra-articular ligamentous structures but also by periarticular soft tissues (Mayr et al., 2024; Vap et al., 2017), skin movement (Gimm et al., 2026) and the effectiveness of limb fixation during testing (Musahl et al., 2010). Greater stabilization likely reduces accessory motion of surrounding soft tissues and minimizes unintended movement of the entire limb segment, thereby decreasing the measured rotational excursion. This suggests that part of the measured rotational laxity may represent non-articular motion rather than true tibiofemoral rotation. In other words, part of the observed rotational displacement may reflect soft tissue compliance or slight limb movement rather than pure joint motion.

This interpretation is particularly important in the context of instrumented arthrometry, where the precision of rotational measurements depends on fixation of the lower limb (Gimm et al., 2026). Previous literature has emphasized that rotational laxity is highly variable and influenced by measurement setup, flexion angle, and sensor location (Mouton et al., 2016). The present findings further support the need for rigorous standardization of stabilization procedures, especially when rotational parameters are used for clinical decision-making or research comparisons.

From a clinical perspective, these findings may have direct implications for the use of the DYNEELAX® arthrometer and similar devices. While minor variations in stabilization force may not substantially affect anterior laxity outcomes, they appear to have a measurable effect on rotational assessments. This suggests that clinicians and researchers should pay particular attention to maintaining consistent stabilization force during rotational testing to improve measurement validity, reliability and comparability between sessions and examiners. This may be especially relevant in the evaluation of ligamentous injuries involving rotational instability, such as anterior cruciate ligament insufficiency or combined anterolateral complex injuries.

Although the present study does not permit determination of an optimal stabilisation force threshold, the observed inverse association between stabilisation force and rotational laxity suggests that greater stabilisation may improve the precision and consistency of rotational measurements. During testing, participants were instructed to remain relaxed, while stabilisation forces were standardised between 80 and 150 N according to participant tolerance. In functional conditions, however, muscular forces acting around the knee joint are substantially greater than the externally applied stabilisation forces used during arthrometry. Therefore, insufficient fixation may allow additional accessory movement of the limb and surrounding soft tissues, potentially contributing to increased measured rotational displacement. From a methodological perspective, these findings suggest that higher and well-standardised stabilisation forces may be preferable when assessing rotational knee laxity.

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes causal inferences. Second, the sample consisted exclusively of healthy young

adults, limiting generalizability to injured and older populations. Third, although measurements followed standardized procedures, all assessments were conducted by a single examiner, which may reduce external validity despite prior training and pilot reliability testing. Fourth, electromyography (EMG) was not used to verify whether participants were fully relaxed during the assessments.

Future studies should investigate whether the observed relationship between stabilization force and rotational laxity is also present in individuals with ligamentous injuries, particularly anterior cruciate ligament-deficient knees, where rotational instability is often clinically relevant. Furthermore, establishing an optimal and standardized stabilization force range may contribute to improved reproducibility of rotational knee laxity measurements across different arthrometers and clinical settings.

In conclusion, the present study demonstrated that knee joint stabilization force is moderately and inversely associated with mediolateral rotational laxity, while no meaningful relationship was observed with anterior laxity. These findings underscore the importance of standardized stabilization procedures, particularly for rotational knee laxity assessment, and provide clinically relevant information for improving the precision of instrumented knee joint evaluation.

5. Conclusions

This study examined the relationship between knee joint stabilization force and anterior and mediolateral rotational knee laxity in healthy young adults using the DYNEELAX® arthrometer. The results showed no significant association between stabilization force and anterior knee laxity, indicating that anterior laxity measurements are relatively robust to variations in external fixation within the tested range. In contrast, mediolateral rotational laxity showed consistent moderate inverse associations with stabilization force, indicating that higher stabilization is associated with lower measured rotational displacement.

These findings suggest that rotational laxity is more sensitive to testing conditions than anterior laxity, likely reflecting the greater contribution of periarticular soft tissues and the dependence of rotational measurements on effective limb fixation. From a clinical and methodological perspective, this underscores the importance of maintaining consistent and well-controlled stabilization procedures, particularly when assessing rotational knee laxity.

Overall, stabilization force appears to be a relevant factor associated with rotational, but not anterior, knee laxity. Ensuring standardized testing conditions may therefore improve the accuracy, validity, and comparability of instrumented knee joint measurements in both research and clinical practice.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-436/2024-2711-3). All procedures were performed in accordance with relevant guidelines and regulations, and informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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