Editorial

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Bioengineered Grafts and Their Potential Applications in Advancing Knee Anterior Cruciate Ligament Reconstructive Surgery

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The introduction of synthetic materials for the reconstruction of the anterior cruciate ligament (ACL) in the 20th century, appeared as an attractive alternative to traditional autologous and allogenic tissues, given the absence of donor site morbidity and potential disease transmission.

However, every new artificial ligament introduced to the market, after initial promising results, failed to gain widespread acceptance in clinical practice due to considerable adverse effects, in most cases leading to withdrawal after approval by regulatory entities [1]. As a result of the loss of trust by the scientific community, the development of new synthetic grafts was stagnant for decades.

At present, few artificial ligaments are still available on the market, and their use is limited [2]. Issues regarding their mechanical and biological properties are still present, as existing synthetic substitutes lack the biological complexity of the native ACL, posing inherent risks of loosening and foreign-body complications from wear debris [3].

To overcome these issues, biomedical engineering, a multidisciplinary field at the intersection of biology, engineering, and medicine, is working on refining artificial graft features to replicate the native human ACL, offering the potential for improved outcomes and accelerated patient recovery [4].

With the goal of enhancing mechanical properties and biocompatibility of synthetic grafts, surface modification methods have been introduced to create bio-enhanced scaffolds, aiming to increase osseointegration at the bone/ligament interface [5]. By tailoring scaffolds to reproduce the native ACL structure and composition, tissue-engineering can promote cell migration and differentiation, allowing tissue regeneration.

Stem cells have been utilized on the surface of bio-enhanced scaffolds in animal trials, showing good capacity in improving tendon-bone regeneration [6]. Among the various types of stem cells, ligament stem/progenitor cells have demonstrated potential in generating tendon/ligament lineage cells [6]; bone marrow-derived mesenchymal stem cells promoted accelerated healing and tissue regeneration when employed on the surface of bio-enhanced scaffolds [7]. Several bioactive coatings able to promote cell proliferation and healing potential have been tested *in vitro* and on animal studies. Silk fibroin, graphene, bioactive glass, and hydroxyapatite are among the polymers used to enhance angiogenesis and osteogenesis, ultimately allowing graft-to-bone healing after ACL surgery [8,9].

Recent advancements include the exploration of innovative bio-based polymers with enhanced tensile strength and delayed biodegradation [10]. Bioabsorbable artificial ligaments gradually degrade over time, while maintaining structural integrity during crucial phases of ligament recovery. Polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid are synthetic biodegradable polymers that exhibit good biocompatibility and rare foreign body reactivity. Because of their biocompatibility and capacity to create an extracellular matrix resembling native ligaments, natural polymers are appealing for use as bioactive scaffolds. The scaffolds can be digested by the biological environment thanks to their ability to cause hydrolytic breakdown, which limits toxicity and chronic immunological reactions. Natural polymers, despite these benefits, have a poor mechanical profile, which restricts their use in tissue engineering [4].

While tissue-engineered grafts may have certain advantages over conventional grafting methods, it is important to consider risks, drawbacks, and uncertainties associated with their application.

The biological responses and mechanical properties of tissue-engineered grafts when applied to ACL reconstruction *in vivo* remain unknown. The safety profile of these devices still still needs elucidation in the clinical setting, including evaluating potential issues that may cause serious side effects.

Still the mechanical properties of tissue-engineered grafts must be improved to match those of the native ACL in order to ensure long-term stability and usefulness. Incomplete tissue maturation leading to graft failure, or inflammatory reactions promoted by debris degeneration are concerns that should be addressed in further *in vivo* research.

Enhancing biocompatibility to reduce unpleasant reactions, inflammation, and responses to foreign bodies remains a challenge. In addition, tissue-engineered grafts must pass rigorous clinical studies and receive regulatory approval before use in patients. Obtaining regulatory approval and widespread clinical acceptance are difficult due

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to the complexity of tissue engineering and the need for long-term follow-up, safety evaluations, and comparison studies with conventional grafting techniques. Eventually, due to the significant expenses involved in research, development, and manufacture, tissue-engineered grafts may impose financial restrictions. Furthermore, the availability of tissue-engineered grafts in areas with inadequate healthcare infrastructure or in resource-constrained settings can present considerable obstacles to their deployment, limiting their potential worldwide impact.

Nonetheless, there are also excellent examples of strategies for overcoming current obstacles to clinical translation.

Bioengineering advances have recently resulted in the creation of biomimetic scaffolds that emulate the natural ACL's microenvironment. Various technologies, including 3D bioprinting, electrospinning, and cell sheets, have been used in ligament and tendon engineering [11,12], enabling technologies enable the precise placement of various cell types and growth factors to replicate the anatomical structure of the natural ACL.

In addition, ACL-on-a-chip systems have been developed, where cells are cultivated within microfluidic channels, allowing the replication of parameters (pH, flow, pressure, and nutrients) found *in vivo*, which sustain cell proliferation [13].

Furthermore, nanotechnology could offer novel solutions to optimize graft-host tissue integration enhance graft strength and promote tissue integration. The high surface area-to-volume ratio of nanofibers enhances cellular interactions, closely mirroring the mechanical characteristics of native ligaments [14].

Additionally, integrating 3D printing could allow fabrication of patient-specific implants, tailoring the design to individual anatomical variations. This personalized approach is crucial in achieving biomimicry, as the printed ligaments closely resemble the architecture of the native ACL. As a result, the 3D-printed ligaments offer improved biomechanical properties, reducing the risk of graft failure and enhancing long-term stability [15].

Ultimately, reduced surgery time, shorter hospital stays, faster recovery time, and—most importantly—a lower rate of re-ruptures might all justify higher expenses brought by regenerative medicine, highlighting long-term advantages and ultimately overcoming financial limitations.

In the future, advancements in material science and genetic modification could open novel avenues for regenerative engineering, leading to the development of bioengineered grafts with dynamic mechanical properties and self-healing features, thus bridging the gap in current clinical challenges.

In conclusion, although tissue-engineered grafts show promise for ACL restoration surgery, careful consideration of concerns, challenges, and restrictions is crucial. Further research and development focusing on scaffold design, cellular source, graft integration, immunogenicity, regulatory approval, and cost accessibility are crucial for advancing ACL reconstruction and enhancing patient care. Addressing these aspects will contribute to the safety, efficacy, and long-term success of bioengineered grafts.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding author if needed.

Author Contributions

Conceptualization, CL and AV; methodology, CL and AV; resources, AV; writing-original draft preparation, CL; writing-review and editing, AV; visualization, CL; supervision, AV. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Claudio Legnani is serving as one of the Editorial Board members of this journal. We declare that Claudio Legnani had no involvement in the peer review of this article and has no access to information regarding its peer review.

References

[1] Legnani C, Ventura A, Terzaghi C, Borgo E, Albisetti W. Anterior cruciate ligament reconstruction with synthetic grafts. A review of literature. International Orthopaedics. 2010; 34: 465–471.

[2] Marieswaran M, Jain I, Garg B, Sharma V, Kalyanasundaram D. A Review on Biomechanics of Anterior Cruciate Ligament and Materials for Reconstruction. Applied Bionics and Biomechanics. 2018; 2018: 4657824.

[3] Tulloch SJ, Devitt BM, Norsworthy CJ, Mow C. Synovitis following anterior cruciate ligament reconstruction using the LARS device. Knee Surgery, Sports Traumatology, Arthroscopy. 2019; 27: 2592–2598.

[4] Legnani C, Ventura A. Synthetic grafts for anterior cruciate lig-

ament reconstructive surgery. Medical Engineering & Physics. 2023; 117: 103992.

[5] Li H, Chen S. Biomedical coatings on polyethylene terephthalate artificial ligaments. Journal of Biomedical Materials Research. Part A. 2015; 103: 839–845.

[6] Wang C, Hu Y, Zhang S, Ruan D, Huang Z, He P, *et al*. Application of Stem Cell Therapy for ACL Graft Regeneration. Stem Cells International. 2021; 2021: 6641818.

[7] Huang J, Chen F, Jian G, Ye Z, Wang Z, Liu H, *et al*. Effect of culture complex of BMSCs and sodium hydroxide- and GRGDSPC-treated PET on the reconstruction of injured anterior cruciate ligament in a rabbit model. International Journal of Clinical and Experimental Medicine. 2015; 8: 6902–6913.

[8] Wang S, Ge Y, Ai C, Jiang J, Cai J, Sheng D, *et al*. Enhance the biocompatibility and osseointegration of polyethylene terephthalate ligament by plasma spraying with hydroxyapatite in vitro and in vivo. International Journal of Nanomedicine. 2018; 13: 3609–3623.

[9] Cai J, Zhang Q, Chen J, Jiang J, Mo X, He C, *et al*. Electrodeposition of calcium phosphate onto polyethylene terephthalate artificial ligament enhances graft-bone integration after anterior cruciate ligament reconstruction. Bioactive Materials. 2020; 6: 783–793.

[10] Kawakami Y, Nonaka K, Fukase N, Amore AD, Murata Y, Quinn P, *et al*. A Cell-free Biodegradable Synthetic Artificial Ligament for the Reconstruction of Anterior Cruciate Ligament in a Rat Model. Acta Biomaterialia. 2021; 121: 275–287.

[11] Shiroud Heidari B, Ruan R, Vahabli E, Chen P, De-Juan-Pardo EM, Zheng M, *et al*. Natural, synthetic and commercially-available biopolymers used to regenerate tendons and ligaments. Bioactive Materials. 2022; 19: 179–197.

[12] Sensini A, Massafra G, Gotti C, Zucchelli A, Cristofolini L. Tissue Engineering for the Insertions of Tendons and Ligaments: An Overview of Electrospun Biomaterials and Structures. Frontiers in Bioengineering and Biotechnology. 2021; 9: 645544.

[13] Bakirci E, Guenat OT, Ahmad SS, Gantenbein B. Tissue engineering approaches for the repair and regeneration of the anterior cruciate ligament: towards 3D bioprinted ACL-on-chip. European Cells & Materials. 2022; 44: 21–42.

[14] Naghieh S, Lindberg G, Tamaddon M, Liu C. Biofabrication Strategies for Musculoskeletal Disorders: Evolution towards Clinical Applications. Bioengineering. 2021; 8: 123.

[15] Touré ABR, Mele E, Christie JK. Multi-layer Scaffolds of Poly(caprolactone), Poly(glycerol sebacate) and Bioactive Glasses Manufactured by Combined 3D Printing and Electrospinning. Nanomaterials. 2020; 10: 626.