

General

Infrapatellar Fat Pad-Derived Non-Cellular Products in Therapy for Musculoskeletal Diseases: A Scoping Review

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Background

The complex nature of musculoskeletal diseases and the limitations of existing treatments have driven researchers to explore innovative solutions, particularly those involving stem cells and their derivatives. The utilization of the IPFP as a source of MSC-derived non-cellular products for the treatment of musculoskeletal diseases has gained recognition in recent years. This study aimed to identify the progress of IPFP-derived acellular biologics use in the treatment of orthopedic conditions such as osteoarthritis and ligament and/or tendon injuries.

Methods

A literature search was conducted through PubMed, Scopus and Google Scholar databases including studies over the past 10 years. This scoping review includes studies discussing the development of intercellular messenger signaling molecules (non-cellular products) in the form of exosomes, secretomes, and conditioned medium derived from the IPFP in the management of musculoskeletal diseases. The PRISMA-ScR guidelines were utilized in this review.

Results

Six studies met the inclusion criteria. Most studies reported the beneficial anti-inflammatory effects of IPFP-derived noncellular products in musculoskeletal conditions. The effects of IPFP-derived exosomes, secretomes, and conditioned medium administration are mostly reported in microscopic changes through cellular and matrix changes. Additionally, quantitative analyses involved assessing levels of anti-inflammatory and pro-inflammatory markers, proteins, fatty acids, and gene expression.

Conclusions

The use of IPFP-derived non-cellular products has shown significant promise in the regenerative therapy for musculoskeletal diseases. These agents have demonstrated beneficial effects, particularly in reducing inflammation, promoting cellular changes, and enhancing tissue regeneration. However, further research is needed to fully understand the characteristics and explore the potential applications of IPFP-derived non-cellular products in musculoskeletal cases.

INTRODUCTION

Musculoskeletal disorders encompass a wide variety of conditions that affect bones, muscles, cartilage, tendons, and ligaments. Symptoms associated with inflammation are frequently present in these conditions, and they can manifest

in a variety of ways, including acute or chronic, local or systemic. In general, they are extremely prevalent and impose a substantial disease burden.¹ Current treatments frequently emphasize the management of symptoms or the replacement of damaged structures, as musculoskeletal components have a restricted capacity to recover from in-

jury. Regenerative medicine, which aims to stimulate the self-regeneration of tissues, offers promising approaches, including cell-based and cell-free therapies. Nowadays, the utilization of culture media/conditioned medium derived from stem cells, and their derivatives is at the forefront of regenerative therapy strategies.^{2,3}

Culture media/conditioned medium contain secretome, which is defined as a large group proteins expressed by cells and secreted into the extracellular space. Secretome consists of soluble proteins (eg. Cytokines, Chemokines, Growth factors, proteases) and extracellular vesicles (eg. Exosome, microvesicle) that may influence numerous cellular physiological functions, such as cell proliferation, differentiation as well as apoptosis. Compared to stem cells, these derivative agents do not contain cellular elements but still hold the key components to communicate between cells. This advantage frees the administration of these biological agents from immune reactions and therapeutic failures due to apoptosis caused by stem cells, without affecting the effects of stimulation of regeneration, immunoregulation, and delivery of bioactive factors.⁴ On the other hand, the widespread application of cell-based treatments is significantly restricted by regulatory issues, and their efficacy may be compromised by cell manipulation.³

Adipose tissue-derived stem cells (ADSC) have become increasingly popular as a secretome source in the tissue engineering process. When compared to traditional bone marrow mesenchymal stem cells and embryonic stem cells, ADSCs provide several significant benefits. These include a higher concentration of cells, easier accessibility, and minimal harm to the patient during the collection process. ADSCs possess the capacity for differentiation in multiple directions. ADSCs, when supported by non-biological scaffolds or cell-free biomaterials and stimulated by external signals like cytokines and environmental cues, can differentiate into several types of tissues including bone, urinary tract, skin, and nerve tissue.⁵

In the search for the ADSC source, infrapatellar fat pad (IPFP) has recently gained attention as a potential adipose tissue source from the musculoskeletal system for the development of targeted secretome utilization. The abundance of dense connective tissue in the IPFP enables it to generate a greater quantity of MSCs in comparison to another source of ADSC. The location of IPFP also serves as a beneficial trait in the regenerative approach, especially for knee-related disease such as osteoarthritis, meniscus tear, and ligament or tendon rupture.

Only a handful of documented studies are available that examined the use of ADSCs concerning musculoskeletal disorders (MSD), and the specificity of IPFP stem cell-derived biologic agents is even more scanty. The goal of this study is to summarize the current state of knowledge on the application of IPFP-derived culture media/conditioned medium, secretome, microvesicle, exosome, or other soluble protein for the regenerative treatment of musculoskeletal disorders.

MATERIAL AND METHODS

The PRISMA-ScR guidelines were utilized in conducting this review, as illustrated in Figure 1. The PRISMA-ScR checklist was first introduced in 2018 to help authors formulate scoping reviews more effectively.⁶ Review protocol was initially submitted to Open Science Framework (OSF) doi: 10.17605/OSF.IO/Q5JNU (link: <https://osf.io/q5jnu/>).

An extensive literature search was performed through PubMed (MEDLINE) and Scopus library on March 2023. The search strategy employed the following terms: (“infrapatellar fat pad” OR “Hoffa pad”) AND (“conditioned medium” OR “secretome” OR “exosome”). This search was restricted to studies published in English within the last decade. To mitigate the potential limitations of these databases, we supplemented our search with a general inquiry on Google Scholar to identify relevant studies not indexed in traditional databases.

This review aims to synthesize findings from studies that investigate the development of intercellular signaling molecules—specifically, non-cellular products such as exosomes, extracellular vesicles (EVs), and other soluble proteins originating from the infrapatellar fat pad (IPFP). Our objective is to delineate advancements in the application of IPFP-derived non-cellular products for the management of musculoskeletal conditions, including osteoarthritis (OA) and ligament/tendon injuries. This review serves as a timely update and a comprehensive checkpoint to facilitate the continued exploration of IPFP-derived biologics.

Our review encompasses both experimental and quasi-experimental study designs, incorporating in vitro and in vivo researches to establish a robust scientific foundation for the application of IPFP-derived non-cellular products, a relatively novel area within regenerative medicine. Furthermore, we considered intervention and descriptive studies, including case-control studies, cross-sectional studies, cohort studies, case series, and case reports, along with other analytical and observational research.

Conversely, we excluded literature reviews, summary reviews, and systematic reviews from this synthesis. Nevertheless, we meticulously reviewed articles cited in these reviews, provided they met our eligibility criteria. Additionally, studies in preprint form were excluded due to concerns regarding the lack of peer review and the associated implications for quality assurance.

Using a data extraction form devised by the reviewers themselves, two separate reviewers collected information from the studies and discussed any disagreements in study inclusion with senior orthopedic and traumatology consultants, resulting in six full texts. Extracted data of interest include author, title, study design, number of participants, model of injury, IPFP preparation, and outcome of interest which involves the application of IPFP-derived secretome/EVs/exosome on musculoskeletal conditions. (Figure 1) Data were collated using Microsoft Excel (Microsoft, Redmond, WA) and presented in a tabular format. The outcome of interest was then extracted as descriptive results. Additionally, we compared the findings from our search strategy to other relevant literature in the discussion section.

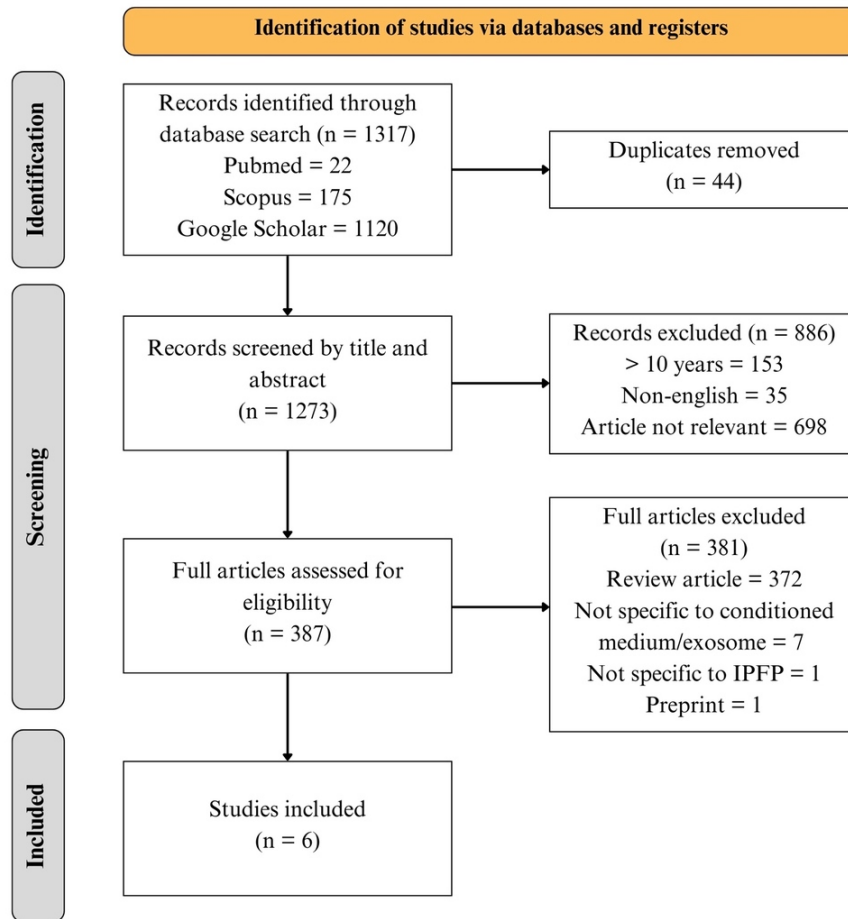


Figure 1. PRISMA-ScR flowchart of study selection⁶

RESULT

Our search strategy resulted in a total of 1,317 articles (22 from PubMed, 175 from Scopus and 1,120 from Google Scholar), and after thoroughly screening the titles and abstracts, we obtained a total of 387 studies. The full articles were then assessed for eligibility by applying inclusion criteria, resulting in six final included studies. (Table 1)

There is an equal number of in-vitro and/or in-vivo within the included studies. All in-vivo studies are of animal subjects (rabbits or rats). Of the 4 studies involving in vivo intervention, 2 were conducted in an OA-induced environment, one in acute synovial/IPFP inflammation, and one in an ACL-reconstruction setting. The majority of IPFP used as exosome or conditioned medium source was taken from OA patients, with one study also comparing the profile of IPFP exosomes to those taken from normal cadaver donors.

Measurement and outcomes varied among studies. The effects of IPFP MSC-derived exosome or conditioned medium administration are mostly reported in microscopic changes through cellular and matrix changes, such as chondrogenic differentiation collagen maturity. Other quantification also includes the measurement of anti- or pro-inflammatory factors, proteins, fatty acids, and gene expressions.

Most studies showed beneficial anti-inflammatory effects of IPFP MSC-derived exosome or conditioned medium administration in these conditions. However, Giermann et al. and Wei et al. both revealed findings that are contradictory to the other studies.^{7,8} These study results stated that exosomes extracted from IPFP of osteoarthritic donors showed lower anti-inflammatory potential compared to the healthy group and IPFP-MSC decreased the gene production related to chondrogenesis.

Outcomes from individual studies are presented in Table 1 along with the study demographics.

DISCUSSION

CELL-FREE VS. STEM CELL THERAPY

In the era of regenerative medicine, researchers are racing to discover the best treatment to be used in promoting tissue regeneration. This technique has a wide range of applications in the treatment of many diseases, including multiple sub branches such as cell and gene therapies and tissue engineering applications.¹³

Over the years, stem cells have been widely used as the best candidate for tissue engineering approaches. However, the administration of stem cells often encountered immune

Table 1. Study demographics

No	Author (year)	Title	Study Design	Number of participant	Model of injury	IPFP preparation	Outcome
1	Gierman et al 2013 ⁷	Metabolic Profiling Reveals Differences in Concentrations of Oxylipins and Fatty Acids Secreted by the Infrapatellar Fat Pad of Donors With End-Stage Osteoarthritis and Normal Donors	In vitro study	46 sample (36 OA 10 post mortem)	NA	FCM from OA	The concentration of Lipoxin A4 in fat conditioned medium (FCM) derived from donors with osteoarthritis is significantly lower as compared to donors without any known health conditions.
2	Wei et al 2015 ⁸	The Infrapatellar Fat Pad From Diseased Joints Inhibits Chondrogenesis of Mesenchymal Stem Cells	In vitro study	13 samples of OA IPFP	NA	IPFP adipose tissue CM	Chondrogenic differentiation and hyaline cartilage matrix formation in MSC are suppressed when IPFP conditioned media is administered to the cells.
3	Shao et al 2021 ⁹	Exosomes from Kartogenin-Pretreated Infrapatellar Fat Pad Mesenchymal Stem Cells Enhance Chondrocyte Anabolism and Articular Cartilage Regeneration	In vitro and Animal in vivo (rabbit)	48 rabbit models (unknown number of rabbits as source of MSC and chondrocyte)	In vivo cartilage defect	IPFP of rabbits pre-treated with kartogenin (KGN) then extracted for their exosome	The chondrogenic differentiation in vitro is improved by exosomes produced from IPFP MSCs, and this enhancement is further augmented by KGN in vivo.
4	Kouroupis et al 2022 ¹⁰	Human infrapatellar fat pad mesenchymal stem cells show immunomodulatory exosomal signatures	In vitro and Animal in vivo (rat)	IPFP from 5 patients	Acute synovial/IPFP inflammation	IPFP MSC exosome	The IPFP exosome has been found to induce synovial hyperplasia, suppress the infiltration of M1 macrophages, and enhance the production of IL-6.
5	Xu et al 2022 ¹¹	Infrapatellar Fat Pad Mesenchymal Stromal Cell-Derived Exosomes Accelerate Tendon-Bone Healing and Intra-articular Graft Remodeling After Anterior Cruciate Ligament Reconstruction	Animal in vivo (rat)	90 rats underwent ACLR using autograft	Unilateral ACLR using autograft	IPFP MSC-derived exosome injection	The utilization of exosomes originating from IPFP has been observed to expedite the process of tendon-bone healing and graft remodeling. This is supported by the discernible enhancement in the maturation and alignment of collagen fibers inside the post-ACLR model.
6	Wu et al 2019 ¹²	miR-100-5p-Abundant Exosomes Derived from Infrapatellar Fat Pad MSCs Protect Articular Cartilage and Ameliorate Gait Abnormalities Via Inhibition of mTOR in Osteoarthritis	Animal in vivo (rat)	unknown numbers of rats	Unilateral destabilization of the medial meniscus to induce OA	MSC IPFP-derived exosome from human with primary OA	In an OA model, IPFP-MSC exosomes significantly reversed the anabolic and apoptotic effects of IL1b, Collagen II, and MMP13 on chondrocytes.

reactions and therapeutic failures caused by their cellular attributes.¹⁴ The rejection rate and uncontrolled growth potential are several setbacks faced by clinicians in utilizing stem cells for therapy. The utilization of MSCs in clinics also faces a great number of restrictions, such as protocols, ethical issues, and policy limitations. Therefore, it is important and necessary to continue the search for a cell-free treatment that could be easier to adapt for use in clinical settings.^{9,15}

Increasing evidence indicates that the secretory products produced by MSC through the paracrine mechanism are largely responsible for the therapeutic benefits of stem cell therapy. Stem cells secrete protein signaling molecules called secretomes, which serve as “communication” vehicles that transport signals from one cell to another. The secretome is a large group of cell secretory products, consisting of soluble protein (eg. Cytokines, Chemokines, Growth factors, proteases) and extracellular vesicles (eg. Exosome, microvesicle). Exosomes have gained widespread acceptance as useful cellular communication vehicles by transporting signals in the form of proteins, lipids, and several types of RNA.¹⁶ The cells that generate exosomes are responsible for regulating their contents, and how exosomes react to their surroundings is a crucial aspect that affects their biological traits and activities. As a direct consequence of this, exosomes have developed into a potentially useful acellular therapeutic agent for tissue regeneration.¹⁷⁻²⁰ MSCs also can secrete beneficial growth factors and cytokines for anti-inflammatory responses including VEGF, TGF- β 1 and IGF-1. Conversely, the pro-inflammatory agents comprise of interleukins (IL-1b, -6, -8, -9) and MMP-3.¹⁸ Although MSC secreted both pro-inflammatory and anti-inflammatory agents, recent evidence suggests that MSC frequently exhibits an overall anti-inflammatory effect.²¹

SOURCE FOCUSING ON ADIPOSE TISSUE SPECIFICALLY IPFP

Adipose tissue is a desirable source to harvest stem cells due to its accessibility and the capability to differentiate into variable lineages. ADSCs are abundant and easily accessible. Adipose tissue, which is present in large quantities throughout the human body, has a substantial number of ADSCs, reaching up to 5000 colony-forming unit–fibroblastic (CFU-F), surpassing BM-MSCs by a factor of 500. ADSCs can be extracted from adipose tissue with just local anesthetic, which reduces patient trauma and ensures an abundant source of stem cells. Furthermore, ADSCs exhibit uncomplicated in vitro culture conditions as a result of their elevated rates of survival and proliferation.⁵ ADSCs have demonstrated a notable resilience to apoptosis in laboratory settings and exhibit greater resistance to oncogenesis. This makes them very promising candidates for cell transplantation therapy, particularly when compared to BM-SCs.²²

The majority of studies stated that utilization of ADSC showed promising improvements reflected by pain and functional measurements.⁹ Additional evidence provided

by Lee et al. suggests that the growth factors and cytokines that are secreted by ADSC-derived MSC can suppress the response of inflammation in the affected joint and prevent chondrocyte death.¹⁸ It also shows a profile that is believed to stimulate tissue regeneration such as ligaments.^{3,23,24}

The infrapatellar fat pad (IPFP) is located in the anterior compartment of the knee joint, which helps preserve the joint cavity by cushioning the knee’s articular surfaces and encouraging the production of synovial fluid.²⁵ This structure is one of the potential sources of ADSC and can be obtained through arthroscopic surgery of the knee or during a total knee replacement procedure.²⁵ Arthroscopic removal of IPFP from patients who are healthy or with osteochondral abnormalities is not expected to aggravate symptoms or impair functions, leading to increased interest in the utilization of exosomes derived from it. In certain instances, it may also obviate the necessity for supplementary surgical interventions, making IPFP a less invasive and less morbidity source of MSC compared to other adipose tissue sources.²⁶⁻²⁸

The IPFP is connected to the tissue around the ACL through microvessels.²⁹ It grows and changes throughout time, just like the synovial area, which contains fibroblasts that perform crucial roles in tissue regeneration. The cell proliferation rate of ADSC derived from human IPFP is relatively high.^{25,29,30}

Another studies by Tangchitphisut et al. and Garcia et al. suggests that MSCs derived from IPFP have a greater chondrogenic and osteogenic differentiation potential than other types of MSCs, as measured by SOX-9 and RUNX-2 expression.^{31,32} This is because of their higher expected processed lipoaspirate cell count, which results from a higher collagenous tissue content. In contrast to this, the collagen content of other types of MSCs is significantly lower.^{9,27,33-36}

MANUFACTURING ADSC (IPFP) DERIVED EXOSOME

Exosomes derived from IPFP MSCs were obtained by first surgically removing and rinsing the fat pad with phosphate-buffered saline. The product was then cut into small pieces followed by a digestion process with a duration of 10 hours in 0.1% type I collagenase. Filtration was then performed by a cell strainer followed by the removal of red blood cells through centrifugation and a red cell lysis buffer. Dulbecco’s modified Eagle’s medium (DMEM), fetal bovine serum (FBS) and penicillin-streptomycin (P/S) were then added with the resulting cells.

The IPFP MSC was left until 70 to 80% confluency was obtained, and was further processed by washing it with PBS two times. The medium was then changed to DMEM with a supplement of exosome-depleted FBS. Following a span of two days, the exosomes were then isolated by collecting the conditioned medium of IPFP MSCs which was further centrifuged. The centrifugation process was done at 4 °C for 10 minutes at 300g proceeded by another 10 minutes at 1500g. After completion, filtration of the supernatant was

performed using a filter of size 0.22- μ m, removing the left-over cells and debris.

Regarding the ultrafiltration method, the supernatant was inserted to an Ultra-clear tube (Millipore) to perform centrifugation for 40 minutes at 4°C at 4000g until volume of the upper compartment has decreased to 200 μ L. The liquid from the ultrafiltration process was resuspended in PBS preceding a repetition of the ultrafiltration process. This was then repeated once more. The final product of exosomes were then kept in aliquots at a temperature of -80 °C.^{11,12}

POTENTIAL OF IPFP-DERIVED BIOLOGICS IN MUSCULOSKELETAL PROBLEMS

Exosomes derived from MSCs have acquired popularity in the field of regenerative sports medicine as a cell-free therapeutic option. Due to the novelty, there is much space for improvement in its application in the field. A literature search focusing on clinical trials published within the past ten years revealed that approximately one-third of the documented studies examined the use of ADSCs with musculoskeletal disorders (MSD). ADSC has been demonstrated to have therapeutic promise for MSD by inhibiting β -galactosidase activity and γ H2AX foci buildup, both of which contribute to the inflammatory response in the affected joint.^{18,19,26}

Researchers have compared intra-articular tissues from patients with inflammatory knee conditions like osteoarthritis (OA) to those from non-inflammatory knees, such as in cases of ligament injury. The goal was to determine which knee condition is most suitable for using the IPFP as a source of MSCs. It was indicated that IPFP stem cells obtained from OA joints have similar chondrogenic capabilities to those obtained from healthy individuals undergoing ligament reconstruction.³³ Other in vitro and in vivo studies by Shao et al. showed that IPFP-derived MSC gathered from OA patients still met the requirements to be considered as a source of mesenchymal cells and were suitable and safe for cartilage repair.⁹

However, an in vitro study by Giermann et al. shows contradictory results. Exosomes extracted from IPFP of osteoarthritic donors showed lower anti-inflammatory potential compared to the healthy group reflected by lower expression of Lipoxin A4 fatty acid. This specific fatty acid targets lower IL-1b concentration, a biomarker commonly found in inflammatory processes such as osteoarthritis or traumatic ruptures of ligaments. In addition, they mentioned that the greater secretion of omega 6 arachidonic fatty acid obtained from the OA-derived IPFP-conditioned medium contributed to the pro-inflammatory characteristics of the OA sample.⁷ Wei et al. concurred with Giermann et al., as IPFP extracted from OA patients failed to demonstrate a knee joint-protective capacity. It was stated that IPFP inhibits chondrogenesis and shifts hyaline cartilage production to fibrocartilage. This condition was postulated due to macrophage activity of the inflammatory environment in OA.⁸

Approximately one-third of studies done by Lee et al. focused on the utilization of ADSCs for various applications, including degenerative causes such as OA and traumatic causes including tendinopathy of Achilles and tear of rotator cuff.¹⁸ IPFP-MSC-derived exosomes showed strong potential as an OA treatment approach in a mouse model, where they promoted chondrocyte proliferation and differentiation, matrix formation, and downregulation of catabolic factors.²⁶ These exosomes also counteract the effects of IL-1b on collagen type II, ADAMTS-5, and MMP-13, thereby inhibiting apoptosis and promoting anabolic processes in chondrocytes.¹² On the other hand, Kouroupis et al. stated that they succeeded in polarizing M1 to M2 macrophages after IPFP MSC exosome therapy in the in-vitro experiment. The M1 phenotype is a pro-inflammatory type of macrophage whereas the M2 macrophage serves as an anti-inflammatory agent.¹⁰ Furthermore, ADSC culture from IPFP has shown protective capability, decreasing inflammatory pain and restoring joint function in people with OA through the effects of exosomes containing miR-100-5p.¹² The injection of IPFP-derived exosomes has been demonstrated as a secure and effective approach with an encouraging outcome in a short-term phase.^{37,38}

Studies have shown that the combination of ADSC-MSC with adjuvants such as platelet-rich plasma (PRP) and hyaluronic acid (HA), can improve symptoms and regenerate meniscal cartilage in patients with meniscal tears.²¹ The generation of cartilaginous tissue by IPFP-derived MSC can be achieved through encapsulation within the agarose cartilage hydrogels.³⁹ The utilization of hydrogel as a mechanical and functional scaffold has been found to augment the effectiveness of exosomes through their retention and controlled release mechanisms, which enable exosomes to maintain their activity within the targeted area for an extended duration.¹⁹ In a laboratory experiment involving cell cultures, the utilization of MSC obtained from the IPFP in combination with nanoparticles made of chitosan and hyaluronic acid demonstrated a beneficial effect on the process of chondrogenic development and has the potential to be used for cartilage repair of OA knee.⁴⁰ Additionally, as compared to exosomes derived solely from IPFP mesenchymal cells, the potential of exosomes that had been previously treated with kartogenin (KGN) before being used demonstrated a significantly enhanced capacity to promote anabolic effects.⁹

USE OF IPFP-DERIVED BIOLOGICS SPECIFICALLY IN LIGAMENT AND TENDON

An anterior cruciate ligament (ACL) rupture is one of the most common knee injuries caused by overstretching of the ligament, which is frequent in sports.⁴¹ A complete ACL rupture necessitates surgery, but there is no standard technique for addressing partial tears.^{42,43}

Even though ACL reconstruction has become the standard treatment for ACL rupture, the rate of complete recovery among patients is still less than 50%.^{44,45} Furthermore, the utilization of patellar tendon grafts for repair differs from the ACL's native form.⁴⁶ These constraints spurred the

investigation of alternate therapeutic approaches, such as stem cells and their derived biologics. Exosomes produced from IPFP-MSCs have been observed to improve healing and graft remodeling after ACL reconstruction in mouse models by immunomodulating macrophage polarization, resulting in the robustness of the graft-to-bone interface.¹²

Rhatomy et al. discovered that secretomes produced from stem cells had a promising effect in improving tendon and ligament healing. In the partial posterior cruciate ligament (PCL) tears in vivo, the use of conditioned medium from Umbilical Cord-derived MSC has successfully stimulated the regeneration and improved knee function.⁴⁷

During tendon healing, exosomes might effectively reduce the inflammatory response, enhance macrophage polarization, and improve the histological features. Exosomes help tendon regeneration through stimulation of tenocyte migration and proliferation that is linked to the activity of TGF-1, VEGFA, and various types of microRNA.^{19,48,49}

There are some limitations in this study. The number of included studies is small and has high heterogeneity in reporting outcomes. Additional research using larger animal models is required to ensure that the findings apply to humans. Exosome approaches should be applied cautiously until their safety and efficacy have been established through clinical trials.

CONCLUSION

IPFP-derived non-cellular products offer a promising avenue for research and clinical application as an alternative to stem cell treatments. By promoting chondrogenesis, reducing inflammation, and enhancing tissue repair, these acellular biologics show potential in various conditions, including osteoarthritis (OA) and ligament/tendon injuries. Among these, IPFP-derived exosomes hold significant promise to revolutionize the treatment landscape for musculoskeletal issues, providing an effective and less invasive option for patients. However, further research, including randomized controlled trials and comparative effectiveness studies, is needed to validate these findings and explore the potential of acellular products in regenerative sports medicine, as current studies on the use of IPFP-derived non-cellular products (exosomes, secretomes, and conditioned

medium) in treating musculoskeletal diseases remain limited.

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ETHICS COMMITTEE

Ethical review and approval were waived for this study as it did not involve human studies

GUARANTOR

AFRT

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT STATEMENT

Not applicable. This study did not involve human studies

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request

AUTHORS CONTRIBUTION

Conceptualization: AFRT. Methodology: AFRT, YWW, PAS. Writing: AFRT, PAS, DAF. AFH Reviewing: AFRT, YWW, WA, RM, IB, PAS, DAF. Editing: AFRT, YWW, WA, RM, IB, PAS, DAF. AFH Supervision: AFRT, YWW, WA, RM, IB. Validation: WA, RM, IB. Data curation: DAF. AFH

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REFERENCES

1. Lamas López JR. Regenerative Medicine applied to treatment of musculoskeletal diseases. *Reumatol Clin*. 2014;10(3):139-140. doi:[10.1016/j.reuma.2014.04.001](https://doi.org/10.1016/j.reuma.2014.04.001)
2. D'Arrigo D, Roffi A, Cucchiaroni M, Moretti M, Candrian C, Filardo G. Secretome and extracellular vesicles as new biological therapies for knee osteoarthritis: A systematic review. *J Clin Med*. 2019;8(11):1867. doi:[10.3390/jcm8111867](https://doi.org/10.3390/jcm8111867)
3. Rhatomy S, Pawitan JA, Kurniawati T, Fiolin J, Dilogio IH. Allogeneic umbilical cord mesenchymal stem cell conditioned medium (secretome) for treating posterior cruciate ligament rupture: A prospective single-arm study. *Eur J Orthop Surg Traumatol*. 2022;33(3):669-675. doi:[10.1007/s00590-022-03278-z](https://doi.org/10.1007/s00590-022-03278-z)
4. Shen H, Yoneda S, Abu-Amer Y, Guilak F, Gelberman RH. Stem cell-derived extracellular vesicles attenuate the early inflammatory response after tendon injury and Repair. *J Orthop Res*. 2019;38(1):117-127. doi:[10.1002/jor.24406](https://doi.org/10.1002/jor.24406)
5. Dong L, Li X, Leng W, et al. Adipose stem cells in tissue regeneration and repair: From bench to bedside. *Regen Ther*. 2023;24:547-560. doi:[10.1016/j.reth.2023.09.014](https://doi.org/10.1016/j.reth.2023.09.014)
6. Tricco AC, Lillie E, Zarin W, et al. Prisma extension for scoping reviews (PRISMA-SCR): Checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:[10.7326/m18-0850](https://doi.org/10.7326/m18-0850)
7. Gierman LM, Wopereis S, van El B, et al. Metabolic profiling reveals differences in concentrations of oxylipins and fatty acids secreted by the infrapatellar fat pad of end-stage osteoarthritis and normal donors. *Arthritis Rheum*. Published online 2013. doi:[10.1002/art.38081](https://doi.org/10.1002/art.38081)
8. Wei W, Rudjito R, Fahy N, et al. The infrapatellar fat pad from diseased joints inhibits chondrogenesis of mesenchymal stem cells. *Eur Cell Mater*. 2015;30:303-314. doi:[10.22203/ecm.v030a21](https://doi.org/10.22203/ecm.v030a21)
9. Shao J, Zhu J, Chen Y, et al. Exosomes from kartogenin-pretreated infrapatellar fat pad mesenchymal stem cells enhance chondrocyte anabolism and articular cartilage regeneration. *Stem Cells Intl*. 2021;2021:1-12. doi:[10.1155/2021/6624874](https://doi.org/10.1155/2021/6624874)
10. Kouroupis D, Kaplan LD, Best TM. Human infrapatellar fat pad mesenchymal stem cells show immunomodulatory exosomal signatures. *Scientific Reports*. 2022;12(1). doi:[10.1038/s41598-022-07569-7](https://doi.org/10.1038/s41598-022-07569-7)
11. Xu J, Ye Z, Han K, et al. Infrapatellar fat pad mesenchymal stromal cell-derived exosomes accelerate tendon-bone healing and intra-articular graft remodeling after Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. 2022;50(3):662-673. doi:[10.1177/03635465211072227](https://doi.org/10.1177/03635465211072227)
12. Wu J, Kuang L, Chen C, et al. Mir-100-5p-abundant exosomes derived from infrapatellar fat pad mscs protect articular cartilage and ameliorate gait abnormalities via inhibition of mtor in osteoarthritis. *Biomaterials*. 2019;206:87-100. doi:[10.1016/j.biomaterials.2019.03.022](https://doi.org/10.1016/j.biomaterials.2019.03.022)
13. Foo JB, Looi QH, Chong PP, et al. Comparing the therapeutic potential of stem cells and their secretory products in Regenerative Medicine. *Stem Cells Int*. 2021;2021:1-30. doi:[10.1155/2021/2616807](https://doi.org/10.1155/2021/2616807)
14. Veronesi F, Borsari V, Sartori M, Orciani M, Mattioli-Belmonte M, Fini M. The use of cell conditioned medium for musculoskeletal tissue regeneration. *J Cell Physiol*. 2017;233(6):4423-4442. doi:[10.1002/jcp.26291](https://doi.org/10.1002/jcp.26291)
15. Wnorowski A, Yang H, Wu JC. Progress, obstacles, and limitations in the use of stem cells in organ-on-a-chip models. *Adv Drug Deliv Rev*. 2019;140:3-11. doi:[10.1016/j.addr.2018.06.001](https://doi.org/10.1016/j.addr.2018.06.001)
16. Connor DE, Paulus JA, Dabestani PJ, et al. Therapeutic potential of exosomes in rotator cuff tendon healing. *J Bone and Miner Metab*. 2019;37(5):759-767. doi:[10.1007/s00774-019-01013-z](https://doi.org/10.1007/s00774-019-01013-z)
17. Lee WY, Wang B. Cartilage repair by mesenchymal stem cells: Clinical trial update and Perspectives. *J Orthop Translat*. 2017;9:76-88. doi:[10.1016/j.jot.2017.03.005](https://doi.org/10.1016/j.jot.2017.03.005)
18. Lee S, Chae DS, Song BW, et al. ADSC-based cell therapies for musculoskeletal disorders: A review of recent clinical trials. *Int J of Mol Sci*. 2021;22(19):10586. doi:[10.3390/ijms221910586](https://doi.org/10.3390/ijms221910586)
19. Zhou Q, Cai Y, Jiang Y, Lin X. Exosomes in osteoarthritis and cartilage injury: Advanced Development and potential therapeutic strategies. *Intl J of Biol Sci*. 2020;16(11):1811-1820. doi:[10.7150/ijbs.41637](https://doi.org/10.7150/ijbs.41637)
20. Zou J, Yang W, Cui W, et al. Therapeutic potential and mechanisms of mesenchymal stem cell-derived exosomes as bioactive materials in tendon-bone healing. *J Nanobiotechnology*. 2023;21(1). doi:[10.1186/s12951-023-01778-6](https://doi.org/10.1186/s12951-023-01778-6)

21. Torres-Torrillas M, Rubio M, Damia E, et al. Adipose-derived mesenchymal stem cells: A promising tool in the treatment of musculoskeletal diseases. *Int J Mol Sci.* 2019;20(12):3105. doi:[10.3390/ijms20123105](https://doi.org/10.3390/ijms20123105)
22. Huri PY, Hamsici S, Ergene E, Huri G, Doral MN. Infrapatellar Fat Pad-Derived Stem Cell-Based Regenerative Strategies in Orthopedic Surgery. *Knee Surg Relat Res.* 2018;30(3):179-186. doi:[10.5792/ksrr.17.061](https://doi.org/10.5792/ksrr.17.061)
23. Jung P, Sato T, Merlos-Suárez A, et al. Isolation and in vitro expansion of human colonic stem cells. *Nat Med.* 2011;17(10):1225-1227. doi:[10.1038/nm.2470](https://doi.org/10.1038/nm.2470)
24. Noverina R, Widowati W, Ayuningtyas W, et al. Growth factors profile in conditioned medium human adipose tissue-derived mesenchymal stem cells (CM-hatmscs). *Clinical Nutrition Experimental.* 2019;24:34-44. doi:[10.1016/j.clnex.2019.01.002](https://doi.org/10.1016/j.clnex.2019.01.002)
25. Sun Y, Chen S, Pei M. Comparative advantages of infrapatellar fat pad: An emerging stem cell source for regenerative medicine. *Rheumatology (Oxford).* 2018;57(12):2072-2086. doi:[10.1093/rheumatology/kex487](https://doi.org/10.1093/rheumatology/kex487)
26. Liao HJ, Chang CH, Huang CYF, Chen HT. Potential of using infrapatellar-fat-pad-derived mesenchymal stem cells for therapy in degenerative arthritis: Chondrogenesis, exosomes, and transcription regulation. *Biomolecules.* 2022;12(3):386. doi:[10.3390/biom12030386](https://doi.org/10.3390/biom12030386)
27. Dragoo JL, Samimi B, Zhu M, et al. Tissue-engineered cartilage and bone using stem cells from human infrapatellar fat pads. *J Bone Joint Surg Br.* 2003;85-B(5):740-747. doi:[10.1302/0301-620x.85b5.13587](https://doi.org/10.1302/0301-620x.85b5.13587)
28. Vahedi P, Moghaddamshahabi R, Webster TJ, et al. The Use of Infrapatellar Fat Pad-Derived Mesenchymal Stem Cells in Articular Cartilage Regeneration: A Review. *Int J Mol Sci.* 2021;22(17):9215. doi:[10.3390/ijms22179215](https://doi.org/10.3390/ijms22179215)
29. Maekawa K, Furukawa H, Kanazawa Y, Hijioka A, Suzuki K, Fujimoto S. Electron and immunoelectron microscopy on healing process of the rat anterior cruciate ligament after partial transection: the roles of multipotent fibroblasts in the synovial tissue. *Histol Histopathol.* 1996;11(3):607-619.
30. Peng L, Jia Z, Yin X, et al. Comparative analysis of mesenchymal stem cells from bone marrow, cartilage, and adipose tissue. *Stem Cells Dev.* 2008;17(4):761-774. doi:[10.1089/scd.2007.0217](https://doi.org/10.1089/scd.2007.0217)
31. Tangchitphisut P, Srikaew N, Numhom S, et al. Infrapatellar Fat Pad: An alternative source of adipose-derived mesenchymal stem cells. *Arthritis.* 2016;2016:1-10. doi:[10.1155/2016/4019873](https://doi.org/10.1155/2016/4019873)
32. Garcia J, Mennan C, McCarthy HS, Roberts S, Richardson JB, Wright KT. Chondrogenic Potency Analyses of Donor-Matched Chondrocytes and Mesenchymal Stem Cells Derived from Bone Marrow, Infrapatellar Fat Pad, and Subcutaneous Fat. *Stem Cells Int.* 2016;2016:6969726. doi:[10.1155/2016/6969726](https://doi.org/10.1155/2016/6969726)
33. do Amaral RJ, Almeida HV, Kelly DJ, O'Brien FJ, Kearney CJ. Infrapatellar fat pad stem cells: From developmental biology to cell therapy. *Stem Cells Int.* 2017;2017:1-10. doi:[10.1155/2017/6843727](https://doi.org/10.1155/2017/6843727)
34. Hernugrahanto KD, Dinda Sedar JAM, Santoso D, et al. Infrapatellar Fat Pad-Derived Mesenchymal Stem Cells as an Alternative Cell Source for Cell-based Osteoarthritis Treatment: A Systematic Review on Preclinical and Clinical Evidence. *Malaysian Journal of Medicine and Health Sciences.* 2021;17:58-64.
35. Li Q, Tang J, Wang R, et al. Comparing the chondrogenic potential in vivo of autogeneic mesenchymal stem cells derived from different tissues. *Artif Cells, Blood Substit, Immobil Biotechnol.* 2010;39(1):31-38. doi:[10.3109/10731191003776769](https://doi.org/10.3109/10731191003776769)
36. Masuoka K, Asazuma T, Hattori H, et al. Tissue engineering of articular cartilage with autologous cultured adipose tissue-derived stromal cells using atelocollagen honeycomb-shaped scaffold with a membrane sealing in rabbits. *J Biomedical Mater Res B: Appl Biomater.* 2006;79B(1):25-34. doi:[10.1002/jbm.b.30507](https://doi.org/10.1002/jbm.b.30507)
37. Zhong Y, Wang S, Han Y, Wen Y. Recent advance in source, property, differentiation, and applications of infrapatellar fat pad adipose-derived Stem Cells. *Stem Cells Int.* 2020;2020:1-14. doi:[10.1155/2020/2560174](https://doi.org/10.1155/2020/2560174)
38. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee.* 2012;19(6):902-907. doi:[10.1016/j.knee.2012.04.001](https://doi.org/10.1016/j.knee.2012.04.001)
39. Ahearne M, Buckley CT, Kelly DJ. A growth factor delivery system for chondrogenic induction of infrapatellar fat pad-derived stem cells in fibrin hydrogels. *Biotechnol Appl Biochem.* 2011;58(5):345-352. doi:[10.1002/bab.45](https://doi.org/10.1002/bab.45)

40. Huang S, Song X, Li T, et al. Pellet Coculture of osteoarthritic chondrocytes and infrapatellar fat pad-derived mesenchymal stem cells with chitosan/hyaluronic acid nanoparticles promotes chondrogenic differentiation. *Stem Cell Res Ther.* 2017;8(1). doi:[10.1186/s13287-017-0719-7](https://doi.org/10.1186/s13287-017-0719-7)
41. Cimino F, Volk BS, Setter D. Anterior cruciate ligament injury: diagnosis, management, and prevention. *Am Fam Physician.* 2010;82(8):917-922.
42. Kon E, Di Matteo B, Altomare D, et al. Biologic agents to optimize outcomes following ACL repair and Reconstruction: A systematic review of clinical evidence. *J Orthop Res.* 2022;40(1):10-28. doi:[10.1002/jor.25011](https://doi.org/10.1002/jor.25011)
43. Kobayashi H, Kanamura T, Koshida S, et al. Mechanisms of the anterior cruciate ligament injury in sports activities: A twenty-year clinical research of 1,700 athletes. *J Sports Sci Med.* 2010;9(4):669-675.
44. Hospodar MS, Miller MD. Controversies in ACL reconstruction: Bone-patellar tendon-bone anterior cruciate ligament reconstruction remains the gold standard. *Sports Med Arthrosc Rev.* 2009;17(4):242-246. doi:[10.1097/jsa.0b013e3181c14841](https://doi.org/10.1097/jsa.0b013e3181c14841)
45. Biau DJ, Tournoux C, Katsahian S, Schranz P, Nizard R. ACL reconstruction: a meta-analysis of functional scores. *Clin Orthop Relat Res.* 2007;458:180-187. doi:[10.1097/blo.0b013e31803dcd6b](https://doi.org/10.1097/blo.0b013e31803dcd6b)
46. Abe S, Kurosaka M, Iguchi T, Yoshiya S, Hirohata K. Light and electron microscopic study of remodeling and maturation process in autogenous graft for Anterior Cruciate Ligament Reconstruction. *Arthroscopy.* 1993;9(4):394-405. doi:[10.1016/s0749-8063\(05\)80313-5](https://doi.org/10.1016/s0749-8063(05)80313-5)
47. Rhatomy S, Prasetyo TE, Setyawan R, et al. Prospect of stem cells conditioned medium (secretome) in ligament and tendon healing: A systematic review. *Stem Cells Transl Med.* 2020;9(8):895-902. doi:[10.1002/sctm.19-0388](https://doi.org/10.1002/sctm.19-0388)
48. Cui H, He Y, Chen S, Zhang D, Yu Y, Fan C. Macrophage-derived MIRNA-containing exosomes induce peritendinous fibrosis after tendon injury through the mir-21-5p/smad7 pathway. *Mol Ther - Nucleic Acids.* 2019;14:114-130. doi:[10.1016/j.omtn.2018.11.006](https://doi.org/10.1016/j.omtn.2018.11.006)
49. Ye T, Chen Z, Zhang J, et al. Large extracellular vesicles secreted by human iPSC-derived mscs ameliorate tendinopathy via regulating macrophage heterogeneity. *Bioact Mater.* 2023;21:194-208. doi:[10.1016/j.bioactmat.2022.08.007](https://doi.org/10.1016/j.bioactmat.2022.08.007)