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SYSTEMATIC REVIEWS

Current status of nanofat in the management of knee osteoarthritis: A systematic review

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Abstract

BACKGROUND

Osteoarthritis (OA) is a prevalent joint disorder requiring innovative treatment approaches.

AIM

To evaluate the use of nanofat, a specialized form of adipose tissue-derived cells, in the treatment of OA, by examining its efficacy, safety profile, mechanisms of action, comparative effectiveness, and long-term outcomes.

METHODS

A comprehensive review of preclinical studies, clinical trials, and *in vitro* investigations was conducted. The included studies provided insights into the potential role of nanofat in OA treatment, addressing its efficacy, safety profile, mechanisms of action, comparative effectiveness, and long-term outcomes.

RESULTS

Clinical studies consistently reported the efficacy of nanofat in providing pain relief and functional improvement in patients with OA. Local adverse events were limited to the injection site, such as localized pain and inflammation, and resolved within a few days to weeks. Systemic adverse events were rare, and no significant long-term complications were observed. Mechanistically, nanofat was found to enhance chondrocyte proliferation, reduce inflammation, and promote angioge-

nesis, thereby contributing to its therapeutic effects.

CONCLUSION

Nanofat therapy holds promise as a therapeutic option for managing OA, providing pain relief, functional improvement, and potential tissue regeneration. The safety profile of nanofat treatment appears favorable, but long-term data are still limited. Standardized protocols, larger randomized controlled trials, longer follow-up periods, and cost-effectiveness evaluations are warranted to establish optimal protocols, comparative effectiveness, and long-term outcomes. Despite current limitations, nanofat therapy demonstrates translational potential and should be considered in clinical practice for OA treatment, with careful patient selection and monitoring.

Key Words: Osteoarthritis; Nanofat; Adipose tissue; Cartilage; Knee

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Core Tip: The systematic review establishes that nanofat therapy is a promising intervention for osteoarthritis (OA), offering both pain relief and functional improvement, while also maintaining a favorable safety profile. The therapy's underlying mechanisms include the enhancement of chondrocyte proliferation, reduction of inflammation, and promotion of angiogenesis. Despite these promising findings, the study underscores the need for additional research, particularly in the form of large-scale randomized controlled trials, to validate the long-term efficacy and safety of nanofat therapy in the management of OA.

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INTRODUCTION

Osteoarthritis (OA) is a prevalent degenerative joint disease that primarily affects the articular cartilage, leading to pain, stiffness, and functional impairment[1]. It is a major cause of disability and reduced quality of life, particularly in the elderly population. The pathogenesis of OA involves a complex interplay of mechanical, genetic, and biochemical factors, resulting in the breakdown of cartilage and alterations in joint tissues[2,3]. Current therapeutic approaches for OA mainly focus on symptom management, such as pain relief and improvement of joint function, but there is a growing need for disease-modifying treatments that can promote cartilage repair and slow disease progression[1,4,5].

Adipose tissue consists of small lipid droplets containing various cellular components, including adipose-derived stem cells (ADSCs), microfat (MFAT), nanofat, microvascular fragments (MVF), stromal vascular fraction (SVF), growth factors, cytokines, and exosomes[6]. These cellular elements have demonstrated regenerative properties and can potentially influence tissue repair, modulate the inflammatory response, and stimulate endogenous healing mechanisms [6]. Nanofat can be prepared through a process of mechanical emulsification and filtration, resulting in a suspension of cellular components that can be administered to target tissues[7].

Given their regenerative potential and ability to modulate inflammation, nanofat has garnered attention as a potential therapeutic intervention for various medical conditions, including OA[7,8]. The rationale behind using nanofat in OA treatment lies in its potential to promote cartilage regeneration, reduce inflammation, and provide symptomatic relief[9]. By harnessing the regenerative properties of the cellular components within nanofat, it is hypothesized that they can facilitate tissue repair, restore cartilage homeostasis, and alleviate the clinical manifestations associated with OA. This systematic review on the use of nanofat in OA is warranted to evaluate the existing evidence, elucidate the underlying mechanisms of action, and identify potential benefits and limitations of this emerging therapy. By conducting a rigorous and comprehensive analysis of the available literature, this review provides valuable insights that can guide clinical practice, further research, and the development of novel treatment approaches for OA.

MATERIALS AND METHODS

The protocol for this systematic review was registered in relevant databases. The animal studies protocol was registered in Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies, while the human studies protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews, No. CRD42023437572). Herein, we present a systematic review conducted in accordance with the guidelines of the Back Review Group of Cochrane Collaboration[10] and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[11]. Electronic databases such as PubMed/MEDLINE, EMBASE, Scopus, and Web of Science

were searched using appropriate keywords such as 'nanofat' and Medical Subject Heading terms such as 'osteoarthritis' combined using appropriate Boolean operators. The search strategy was designed to encompass nanofat, OA, and other therapeutic interventions. Additionally, manual searches of reference lists from identified articles and relevant review papers were performed to ensure a comprehensive approach.

Inclusion criteria

The inclusion criteria encompassed studies involving human participants or animal models with OA, interventions using nanofat, comparisons with placebo or other interventions, and outcomes related to cartilage repair, inflammation modulation, pain relief, or joint function improvement (Figure 1). Study designs included *in vitro* studies, animal models, clinical trials, or observational studies.

Exclusion criteria

Studies without nanofat in their comparison arms, those not evaluating at least one of the outcomes of interest, studies exploring the use of nanofat in disease contexts other than OA, and case reports, commentaries, review articles, and editorial articles were excluded.

Study selection process and data extraction

The study selection process involved a two-step approach: (1) Initial screening based on titles and abstracts; and (2) Followed by a detailed full-text assessment of potentially relevant articles. Two independent reviewers conducted the screening process to minimize bias. Any disagreements were resolved through discussion or consultation with a third reviewer if necessary. Data extraction was performed using a predefined template. Extracted information typically included study characteristics (*e.g.*, author, publication year, study design), sample size, intervention details (*e.g.*, nanofat composition, administration method), outcomes measured, follow-up duration, and key findings. Data extraction was also carried out independently by two or more reviewers to ensure accuracy and consistency.

RESULTS

The initial database screening resulted in 161 articles, which after duplicate removal resulted in 122 articles. Following title and abstract screening, 93 articles were excluded to result in 29 articles for full-text screening. Finally, we included nine studies for inclusion in this review. The details of the articles included are presented in Table 1.

Definition and preparation of nanofat

Nanofat, also known as nanofat grafting, is a specialized form of fat grafting that involves the use of emulsified adipose tissue. It is a lipid-based formulation composed of small droplets of adipose tissue-derived cells and extracellular matrix components[6,9]. Unlike traditional fat grafting, where larger clusters of adipocytes are utilized, nanofat employs a refined and emulsified adipose tissue suspension. This process results in a more homogeneous solution containing a higher concentration of regenerative cellular components[12]. The preparation of nanofat involves several key steps to obtain a concentrated suspension of cellular components. Adipose tissue is typically obtained through liposuction or a surgical excision procedure from a suitable donor site, such as the abdomen or thigh[13,14]. A local anesthetic is administered to minimize discomfort during the procedure. The harvested adipose tissue is processed using mechanical emulsification techniques, which involve mechanically disrupting the tissue to break it down into smaller fragments or clusters[15]. The emulsified adipose tissue is then subjected to a filtration process to remove larger cellular debris, connective tissue, and excess lipids. This filtration step helps obtain a more refined and homogeneous solution. In some protocols, centrifugation is performed to separate the different layers of the emulsified adipose tissue, aiding in isolating specific cellular components or achieving further refinement of the nanofat suspension[16,17]. After centrifugation, the nanofat suspension is washed to remove residual local anesthetics, blood, and debris. The suspension is then concentrated by removing excess fluids to obtain a more concentrated cellular component-rich solution. It should be acknowledged that nanofat preparation techniques can vary across studies and practitioners, leading to differences in the composition and characteristics of the final nanofat product (Figure 2). Various factors, including emulsification methods, filtration techniques, centrifugation parameters, and washing protocols, can contribute to these variations, potentially influencing the therapeutic efficacy and outcomes in the treatment of OA.

Composition of nanofat

Nanofat contains several key components and properties that are relevant to its potential therapeutic application in OA treatment. The cellular components within nanofat, such as ADSCs and SVF cells, possess regenerative and immunomodulatory properties. ADSCs can differentiate into various cell lineages, including chondrocytes, which are the building blocks of cartilage[16,18]. These cells have the potential to promote cartilage regeneration and repair damaged joint tissues. SVF cells, on the other hand, contribute to tissue healing, angiogenesis, and modulation of the immune response. Nanofat also contains a range of growth factors and cytokines, such as transforming growth factor beta, platelet-derived growth factor, vascular endothelial growth factor (VEGF), and interleukin (IL)[18,19]. These bioactive molecules play essential roles in cellular communication, inflammation regulation, and tissue repair processes[20,21]. Additionally, nanofat contains extracellular vesicles (exosomes), which are small membrane-bound vesicles released by cells. These exosomes contain bioactive molecules, including microRNAs (miRNAs) and proteins, which can be transferred to

Table 1 Summary of the studies included in systematic review

Ref.	Year	Study type	Samples	Outcomes analyzed	Results	Conclusion
Cicione *et al* [28]	2023	Preclinical *in vitro*	Lipoaspirate from 18 patients	Tissue processing, immunohistochemical analysis, RNA extraction, gene expression analysis	Increased amount of stroma and a reduction of adipocytes in micro-fragmented adipose tissue and nanofat adipose tissue, with the latter displaying the highest content of collagen type I, CD31, CD34 and proliferating cell nuclear antigen with increasing expression of NANOG, Sox2, OCT3/4, COL1A1 and IL-6 without significant differences in terms of IL-1β and inducible nitric oxide synthetase	Micro-fragmented adipose tissue and nanofat adipose tissue techniques allowed the rapid isolation of ASC-rich grafts with a high anabolic and proliferative potential. However, neoadjuvant therapy showed the highest levels of extracellular matrix content, replicating cells, and stemness gene expression
Quintero Sierra *et al*[9]	2023	Preclinical *in vitro*	Nanofat-derived SVF. Non-ASC collagenase-derived ASC. Nanofat-derived-ASC enzymatic digestion of nanofat-SVF	Morphological analysis, cellular yield, proliferation capacity, clonogenic capacity, immunophenotyping, differentiation assay, immunostaining	Hy-Tissue Nanofat is a new, simple system that reduces the time of adipose tissue processing drastically and guarantees the survival of regenerative units	Hy-Tissue Nanofat as a rapid, standardized, and efficient system able to produce an emulsion fat rich in viable, proliferative, and multipotent ASCs, suggesting a potential use in regenerative medicine and tissue engineering when translated into clinical practice
Cohen *et al* [16]	2019	Preclinical *in vitro*	10 patients	Cell counts, cell viabilities, cell cultures, and cell images were taken with a florescent microscope	The LipocubeNano shown to trap more fibrous tissue, with higher cellcounts with equal viability compared to Tulip's NanoTransfer system	Nanofat from LipocubeNano has a higher regenerative cell count and more SVF cells than the other common mechanical method of nanofat processing
Ge *et al*[23]	2023	Preclinical *in vivo*	50 male Sprague-Dawley rats	Paw withdrawal latency, thermal withdrawal latency histopathological and immunohisto-chemical examination, wound healing, and transwell assays were performed to assess effects of nanofat lysate on chondrocytes. RNA-seq, qPCR and Western blot assays were conducted to clarify the mechanism of nanofat lysate	Nanofat lysate significantly improved the proliferation, wound healing, and migration of chondrocytes. It significantly restored the tumor necrosis factor-alpha-altered anabolic markers (Sox9, collagen type II and aggrecan) and catabolic markers (IL-6 and matrix metalloproteinase 13) through transforming growth factor-beta-Smad2/3 signalling pathway	Nanofat lysate from nanofat and demonstrated its therapeutic efficacy of relieving joint pain and cartilage degradation against OA in rats as well as chondroprotective activity of improving cell viability, wound healing, cell migration, and the anabolism/catabolism balance against inflam-matory stress in chondrocytes
Chen *et al*[8]	2021	Preclinical *in vivo*	40 male Sprague-Dawley rats	Pain behaviour evaluation. Histopathological analysis. Immunohistochemical analysis. Transferase dUTP nick end labelling assay	Nanofat promoted the cell viability of chondrocytes, induced wound healing of IL-1β-treated chondrocytes, reversed the abnormal gene expression of IL-1β-treated chondrocytes	Nanofat exerted anti-OA efficacy by ameliorating joint pain symptoms and preventing cartilage degradation of OA rats through paracrine-based actions on anabolic, catabolic, and hypertrophic molecules of chondrocytes
Zheng *et al* [20]	2019	Preclinical *in vivo*	Male BALB/c-nu nude mice	Estimation of mechanism by which fat extract impacts graft survival, the proangiogenic, anti-apoptotic and pro-proliferative activities of fat extract in grafts *in vivo* and in cultured human vascular endothelial cells, adipose-derived stem cells and fat tissue *in vitro*	A higher fat integrity, more viable adipocytes, more CD31-positive blood vessels, fewer apoptotic cells and more Ki67-positive prolif-erating cells were observed in the nanofat-treated and fat extract-treated groups. Fat extract showed proangiogenic effects on HUVECs, anti-apoptotic effects on fat tissue cultured under hypoxic conditions and an ability to promote ADSCs proliferation and maintain their multiple differentiation capacity	Fat extract could improve fat graft survival *via* proangiogenic, anti-apoptotic and pro-prolif-erative effects on ADSCs. Fat extract plus nanofat-assisted fat grafting is a new strategy that could potentially be used in clinical applications
Han *et al*[31]	2022	Preclinical *in vitro* and *in vivo*	Sprague-Dawley rats	Cartilage-targeted retention efficiency, lubrication performance, friction coefficient, gene expression analysis	The microspheres effectively enhanced the cartilage-targeted retention efficiency of nanofat, which also resulted in remarkable lubrication performance, with the friction coefficient being reduced by approximately 80%, which was maintained over time. The three-dimensiona penetrating structure of the microspheres stimulated cytokine secretion by the NF-derived stem cells, upregulating the expression of anabolism-related genes and downregulating	The multifunctional platform with nanofat immobilization and super-lubrication, which showed great potential for the minimally invasive treatment of osteoarthritis

				catabolism, and the expression of inflammation-related and pain-related genes		
Smyshlyaev *et al*[35]	2022	Clinical	70 patients	Physical examination MRI. Adverse events	Decrease in swelling of the surrounding soft tissues with restoration of normal anatomical outlines of the knee joint. Increase in the circumference of the thigh at the level of the lower third. The absence of hyperthermia in the knee joint area. Reduction of pain on palpation of the patella and condyles of the femur and tibia. Increase range of movements. Disappearance of enthesopathies of collateral ligaments and pain in the hamstring muscle tendons. Decrease in the amount of free intra-articular fluid. No serious adverse events noted	Treatment of OA with nanofat is the most effective technique, despite the relatively high cost of obtaining the final cell product
Chen *et al*[8]	2021	Clinical	18 patients	Visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index, MRI	Intra-articular nanofat injections alleviated symptoms and pain in OA patients	The study verified the clinical efficacy and safety of nanofat

ADSCs: Adipose-derived stem cells; ASC: Adherent spleen cells; IL: Interleukin; MRI: Magnetic resonance imaging; OA: Osteoarthritis; Sox: Sex determining region Y-box; SVF: Stromal vascular fraction.

recipient cells and exert therapeutic effects[19,21]. The lipid matrix of nanofat provides a suitable environment for the survival and function of the cellular components, serving as a protective barrier and maintaining the viability of the cells and preserving the bioactive molecules within the nanofat suspension[22].

Mechanism of action of nanofat

Nanofat exerts its therapeutic effects in OA through several mechanisms (Figure 3). One key mechanism is the modulation of inflammation. OA is characterized by chronic low-grade inflammation within the joint, which contributes to the degradation of cartilage and exacerbation of symptoms. Nanofat contains bioactive molecules, including cytokines and growth factors, that possess anti-inflammatory properties. These molecules can suppress the production of pro-inflammatory cytokines, such as IL-1 and tumor necrosis factor-alpha (TNF-α), while promoting the release of anti-inflammatory cytokines, such as IL-10. By shifting the balance towards an anti-inflammatory state, nanofat helps to attenuate inflammation and reduce joint damage[23].

Another mechanism is the promotion of cartilage regeneration. Nanofat contains cellular components, particularly ADSCs, which have the capacity to differentiate into chondrocytes—the specialized cells responsible for producing and maintaining cartilage. When introduced into the joint, the ADSCs within nanofat can home to the damaged areas and differentiate into chondrocyte-like cells[8,24]. These cells can then contribute to the synthesis of new cartilage matrix components, such as collagen and proteoglycans, thereby facilitating cartilage repair and regeneration.

Nanofat also exerts its effects through paracrine signaling and trophic effects. The cellular components within nanofat secrete various bioactive factors, including growth factors, cytokines, and exosomes[7]. These factors can influence neighboring cells, promoting tissue repair by stimulating cell proliferation, angiogenesis (formation of new blood vessels), and extracellular matrix synthesis[25]. Additionally, exosomes released by nanofat cells can transfer miRNAs and other regulatory molecules to recipient cells, modulating their gene expression and promoting regenerative processes.

Furthermore, nanofat possesses immunomodulatory effects. OA is associated with an altered immune response within the joint, characterized by immune cell infiltration and dysregulated cytokine production. The cellular components and bioactive molecules within nanofat can modulate the activity of immune cells, such as macrophages and T cells, leading to a shift from a pro-inflammatory to an anti-inflammatory state[26]. This modulation of the immune response helps to

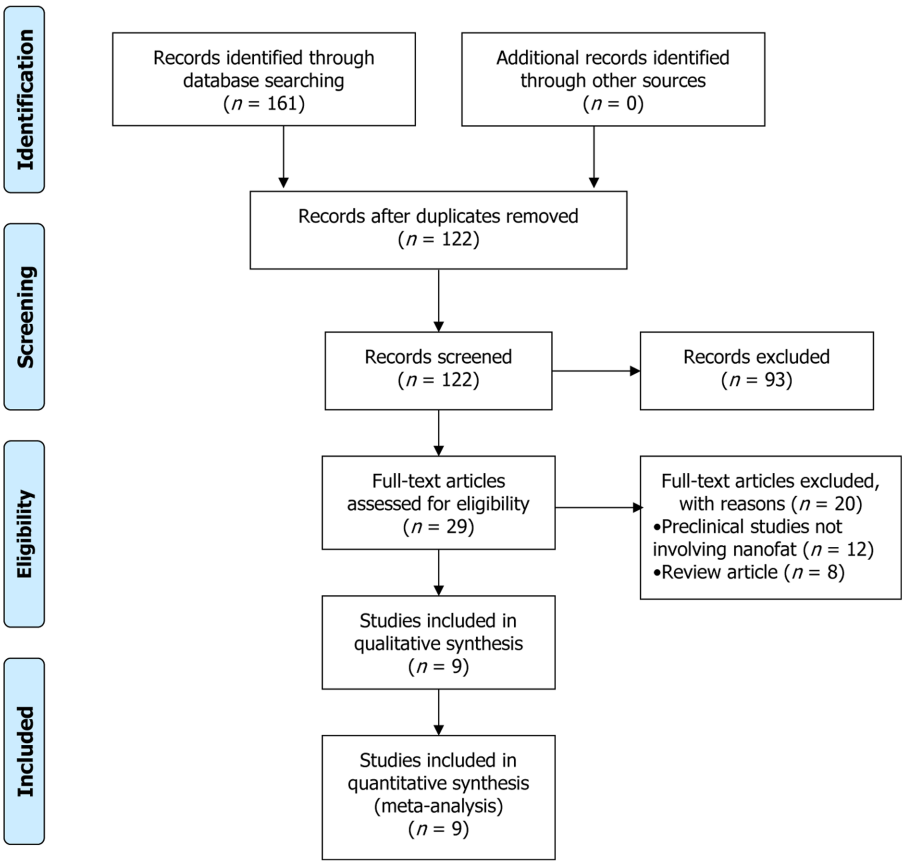


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of included studies in this systematic review.

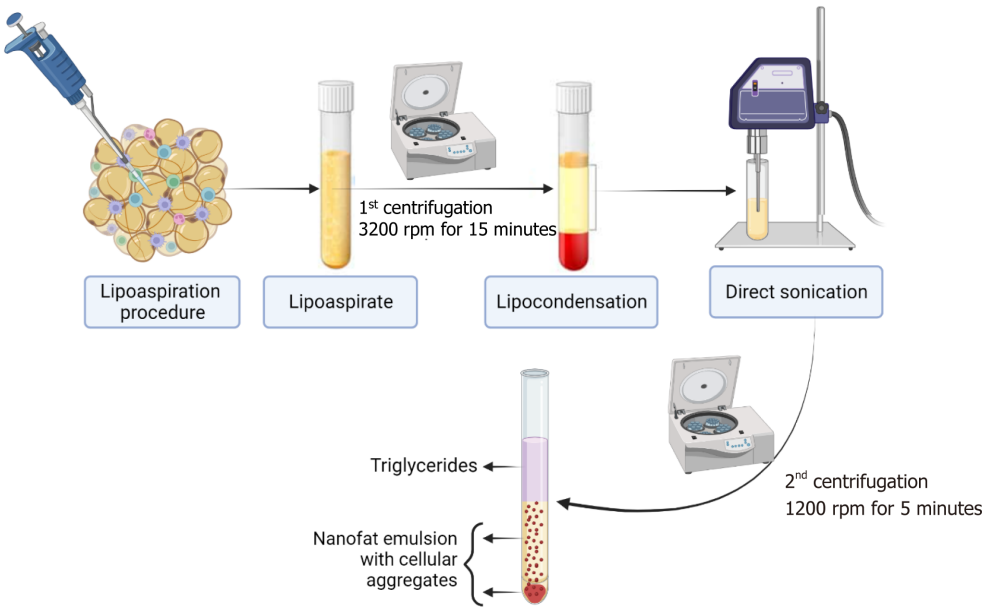


Figure 2 Illustration of a nanofat preparation protocol.

mitigate inflammation, reduce tissue damage, and promote a more favorable environment for cartilage repair.

Pain modulation is another significant mechanism by which nanofat contributes to OA management. Pain is a major symptom in OA, and nanofat may alleviate pain through its anti-inflammatory effects by reducing inflammatory mediators that sensitize pain receptors. Additionally, the secretion of neurotrophic factors by nanofat's cellular components may promote nerve regeneration and modulate pain signaling pathways[27]. The exact mechanisms by which nanofat influences pain perception in OA require further investigation but are likely multifactorial.

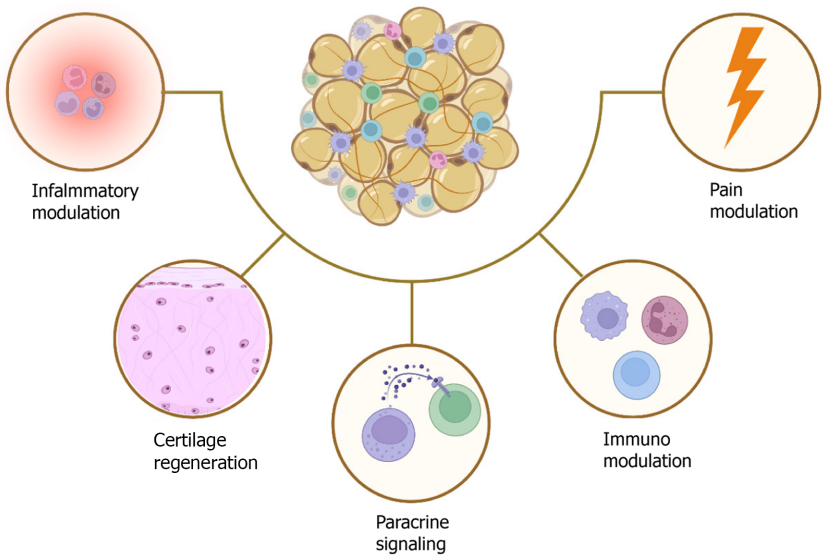


Figure 3 Mechanism of action of nanofat.

Evidence from in vitro and animal studies

In vitro studies exploring the effects of nanofat in OA have provided valuable insights into its regenerative potential. These studies often involve the exposure of cartilage cells (chondrocytes) or other relevant cell types to nanofat-derived factors or direct co-culture with nanofat cells. Several key findings have emerged. First, nanofat-derived factors can stimulate the proliferation and differentiation of chondrocytes[23]. The presence of nanofat-conditioned media or direct co-culture with nanofat cells has been shown to increase chondrocyte viability and promote the synthesis of cartilage-specific extracellular matrix components, such as collagen and proteoglycans[8]. These findings suggest that nanofat has the potential to support cartilage regeneration at the cellular level. Second, *in vitro* investigations have revealed the anti-inflammatory properties of nanofat. Treatment with nanofat-derived factors or co-culture with nanofat cells has been shown to reduce the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, by chondrocytes and other immune cells[28]. Additionally, nanofat has been found to enhance the secretion of anti-inflammatory cytokines, which helps to create a more favorable environment for tissue repair[29]. Third, angiogenesis, the formation of new blood vessels, is a critical process for tissue repair. *In vitro* studies have indicated that nanofat can stimulate angiogenesis by promoting the proliferation and migration of endothelial cells[30]. The factors released by nanofat cells, including VEGF, have been implicated in these pro-angiogenic effects. This suggests that nanofat may facilitate the establishment of a vascular network necessary for cartilage regeneration.

Animal studies have been conducted to further evaluate the potential therapeutic benefits of nanofat in OA. Findings from animal studies have provided valuable insights into the *in vivo* effects of nanofat. One notable observation is the ability of nanofat to promote cartilage repair and regeneration. Histological analysis of cartilage samples from treated animals has revealed improvements in tissue architecture, increased cartilage thickness, and enhanced proteoglycan content. The presence of chondrocyte-like cells derived from nanofat within the repaired cartilage further supports the regenerative potential of nanofat *in vivo*[31]. Additionally, animal models of OA often exhibit joint inflammation similar to that seen in human patients. Studies have shown that nanofat administration can lead to a reduction in inflammatory markers within the joint, including decreased levels of pro-inflammatory cytokines and enzymes[32]. This suggests that nanofat possesses anti-inflammatory properties *in vivo*, contributing to the mitigation of joint inflammation. Moreover, animal studies have assessed the functional outcomes associated with nanofat treatment. Researchers have reported improvements in joint function, as demonstrated by increased weight-bearing capacity, improved gait analysis, and enhanced mobility in animals receiving nanofat treatment. Furthermore, nanofat administration has been associated with reduced pain behaviors and decreased expression of pain-related markers in animal models of OA[8]. However, it is important to note that *in vitro* studies may not fully replicate the complex *in vivo* environment, and animal models, although useful for initial investigations, may not perfectly mimic human OA. Additionally, variations in the specific nanofat preparation techniques and dosage regimens used across different studies make direct comparisons challenging.

Clinical studies

Clinical studies investigating the use of nanofat in the treatment of OA have provided valuable insights into its safety, efficacy, and potential clinical benefits. These studies involve the administration of nanofat directly into the affected joints of patients with OA and the evaluation of various outcomes, including pain relief, functional improvement, and structural changes. Several key findings emerge from these clinical studies. First, the safety and tolerability of nanofat in patients with OA have been consistently reported. The procedure of nanofat injection is generally well-tolerated, with minimal adverse effects[33]. Common side effects, if any, are typically mild and transient, such as temporary swelling, bruising, or discomfort at the injection site[34]. Overall, the safety profile of nanofat appears favorable, making it a viable option for OA treatment. Second, clinical studies have consistently reported significant pain relief and functional

improvement following nanofat treatment in patients with OA. Patients have reported reduced pain scores, decreased analgesic medication requirements, and improved joint function and mobility. These improvements are often observed within a few weeks to months after the nanofat injection and can be sustained for an extended period[35]. The pain relief and functional improvements have a positive impact on patients' quality of life and their ability to perform daily activities. Third, some clinical studies have evaluated the structural changes in joint tissues and the potential for cartilage regeneration following nanofat treatment. Studies have reported evidence of cartilage regeneration and increased cartilage thickness in treated patients[34]. These findings suggest that nanofat may have the potential to promote structural improvements in damaged joint tissues. However, many of these studies have small sample sizes, heterogeneity in patient characteristics, variations in nanofat preparation techniques, and differences in outcome measures, making it challenging to draw definitive conclusions. Moreover, the optimal dosage, treatment frequency, and long-term effects of nanofat treatment remain areas of ongoing research.

Safety and adverse events of nanofat

Ensuring the safety of any medical intervention is paramount, and clinical studies evaluating the use of nanofat in OA have assessed its safety profile and the occurrence of adverse events. Clinical studies have consistently reported a favorable safety profile for nanofat treatment in patients with OA. Local adverse events associated with nanofat treatment are typically limited to the site of injection. These events may include localized pain, tenderness, or inflammation, which are expected reactions to the injection procedure. These effects are generally self-limiting and resolve within a few days to weeks[8,36]. Systemic adverse events, such as allergic reactions or systemic infections, are rare following nanofat treatment[36,37]. Clinical studies have reported no significant systemic adverse events directly attributed to nanofat injection. However, it is essential to maintain proper sterile techniques during the preparation and administration of nanofat to minimize the risk of infection. Long-term safety data for nanofat treatment in OA are still limited due to the relatively recent adoption of this approach. However, the available evidence from follow-up studies ranging from one to several years suggests that nanofat treatment is generally safe and well-tolerated over an extended period. Long-term safety monitoring is crucial to identify any delayed adverse events or complications that may arise.

When considering nanofat treatment, certain precautions should be taken into account. Careful patient selection is crucial to ensure that individuals receiving nanofat treatment are suitable candidates and do not have any contraindications. This may include factors such as underlying medical conditions, allergies, or previous adverse reactions to similar treatments. Nanofat treatment should be performed by qualified healthcare professionals who have experience and expertise in the procedure. Adherence to proper aseptic techniques during the preparation and administration of nanofat is essential to minimize the risk of infection or other complications. Regular monitoring and follow-up of patients who have undergone nanofat treatment are important to evaluate treatment efficacy, assess any potential adverse events, and address any concerns or complications that may arise. In clinical practice and research, it is crucial to report any observed adverse events associated with nanofat treatment accurately. Robust reporting mechanisms ensure the collection and analysis of data on adverse events, contributing to a better understanding of the safety profile of nanofat in OA treatment. This information helps to guide future improvements in safety protocols and enhance patient care.

DISCUSSION

The findings of this systematic review have important implications for clinical practice in the treatment of OA. Nanofat offers a potential therapeutic option that can provide pain relief, functional improvement, and potentially promote tissue regeneration[7]. The regenerative properties of nanofat make it a promising alternative or adjunct to existing treatment modalities. However, further research and clinical trials are required to establish its efficacy, safety, and long-term outcomes. Clinicians should consider the current evidence when making treatment decisions and inform patients about the potential benefits and limitations of nanofat therapy for OA.

A significant aspect that warrants discussion is the comparative effectiveness of nanofat *versus* other fat-based regenerative therapies, particularly MFAT. While both nanofat and MFAT are derived from adipose tissue, they differ in their preparation methods and cellular composition[28,38,39]. MFAT typically involves larger fat particles and may retain more adipocytes and connective tissue, whereas nanofat is processed to a more refined, cell-rich suspension with smaller lipid droplets[28]. This difference in composition may influence their respective regenerative capacities and clinical outcomes. Comparative studies have shown that nanofat appears to provide comparable or superior outcomes in terms of pain relief, functional improvement, and patient-reported outcomes compared to conventional treatments such as hyaluronic acid injections or corticosteroid injections[40]. However, the heterogeneity in study designs, variations in nanofat and MFAT preparation techniques, and the limited number of comparative studies hinder definitive conclusions regarding the relative effectiveness of nanofat compared to other interventions[28,38]. Future studies should include direct comparisons between nanofat and MFAT to elucidate their respective advantages and optimal applications in OA management.

In addition to nanofat and MFAT, other lipid-related regenerative strategies, such as SVF and MVF, are also being explored for OA treatment. SVF contains a heterogeneous mixture of cells, including ADSCs, immune cells, and endothelial progenitor cells, and has been shown to possess immunomodulatory and regenerative properties[6,41]. MVF, which include intact microvessels, can enhance tissue perfusion and support regenerative processes[42,43]. Comparing these different lipid-based therapies, nanofat offers a more refined and cell-dense preparation, potentially enhancing its regenerative and anti-inflammatory effects. However, standardized protocols and head-to-head studies are necessary to determine the most effective lipid-based strategy for OA treatment.

Safety considerations are paramount in the adoption of nanofat therapy. Clinical studies consistently report a favorable safety profile for nanofat treatment in OA, with minimal and transient adverse events. The low incidence of systemic adverse events and the absence of significant long-term complications support the safety of nanofat. However, it is crucial to continue monitoring and reporting adverse events to identify any potential risks associated with nanofat treatment over the long term. Additionally, establishing standardized protocols for nanofat preparation and administration will help ensure consistent safety and efficacy outcomes across different clinical settings.

Long-term outcomes of nanofat treatment are another critical area of focus. Although the long-term effects of nanofat treatment for OA are still being investigated, some studies are showing favorable results. Long-term studies are necessary to determine the durability of the treatment effects and to monitor any potential adverse events or complications over an extended period. Understanding the longevity of pain relief, functional improvement, and tissue regeneration will help in assessing the true therapeutic potential of nanofat in OA management.

Comparative effectiveness and future directions

Comparative studies between nanofat and other treatment modalities have shown promising results. Nanofat appears to provide comparable or superior outcomes in terms of pain relief, functional improvement, and patient-reported outcomes compared to conventional treatments such as hyaluronic acid injections or corticosteroid injections[8]. However, the heterogeneity in study designs, variations in nanofat and MFAT preparation techniques, and the limited number of comparative studies hinder definitive conclusions regarding the relative effectiveness of nanofat compared to other interventions. Further well-designed comparative studies are needed to establish its comparative effectiveness.

Based on the findings of the systematic review, several recommendations can be made for future research and clinical applications. First, conducting well-designed randomized controlled trials is essential to establish the efficacy, optimal dosage, treatment frequency, and long-term outcomes of nanofat treatment in OA. These trials should include standardized protocols for nanofat preparation and administration to ensure consistency and reproducibility of results. Second, investigating the comparative effectiveness of nanofat with other fat-based regenerative therapies, such as MFAT, SVF, and MVF, is necessary to determine their relative advantages and optimal applications in OA management. Third, long-term follow-up studies with extended periods are crucial to assess the durability of treatment effects and identify any delayed adverse events or complications. Fourth, standardizing nanofat preparation techniques will facilitate better comparability between studies and improve the reproducibility of results. Fifth, economic evaluations should be conducted to determine the cost-effectiveness and potential benefits of integrating nanofat into clinical practice compared to other existing regenerative modalities. Sixth, refining patient selection criteria through further research is needed to identify specific patient characteristics or disease profiles that are more likely to benefit from nanofat treatment. Lastly, promoting the robust reporting of adverse events associated with nanofat treatment will contribute to a better understanding of its safety profile through patient-reported online portals and aid in refining safety protocols.

CONCLUSION

This systematic review examined the use of nanofat in OA treatment and synthesized the available evidence. Key findings include the efficacy of nanofat in providing pain relief, functional improvement, and potential tissue regeneration. Mechanisms of action, including enhanced chondrocyte proliferation, anti-inflammatory effects, and angiogenesis promotion, contribute to the therapeutic effects of nanofat. The review also highlighted the safety profile of nanofat, with minimal and transient adverse events reported. However, the review identified gaps in knowledge and the need for further research to establish optimal protocols and long-term outcomes. The evidence supporting the use of nanofat in OA treatment is promising but still evolving. The reviewed studies consistently demonstrate the efficacy of nanofat in reducing pain, improving function, and potentially promoting tissue regeneration. Preclinical and *in vitro* studies provide mechanistic insights into their regenerative properties. However, the evidence is limited by variations in study designs, small sample sizes, and heterogeneity in nanofat and MFAT preparation techniques. Further well-designed randomized controlled trials with larger sample sizes, longer follow-up periods, and standardized protocols are needed to strengthen the evidence base and determine the optimal role of nanofat in OA management.

FOOTNOTES

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