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Review

Advanced methods to mechanically isolate stromal vascular fraction: A concise review

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ABSTRACT

Adipose tissue is a highly attractive reservoir of stem cells due to its accessibility and abundance, and the SVF within it holds great promise for stem cell-based therapies. The use of mechanical methods for SVF isolation from adipose tissue is preferred over enzymatic methods, as it can be readily applied in clinical settings without additional processing steps. However, there is a lack of consensus on the optimal approach for mechanically isolating SVF. This comprehensive review aims to present and compare the latest mechanical isolation methods for SVF from adipose tissue, including centrifugation, filtration/washing, emulsification, vibration, and mincing/adiponizing. Each of these methods possesses unique advantages and limitations, and yet, no conclusive evidence has emerged demonstrating the superiority of one approach over the others, primarily due to the dearth of well-controlled prospective studies in this field.

Contents

1. Introduction

The discovery of adipose-derived stem cells (ASCs) by Zuk et al. [1] has revealed their potential to differentiate into multiple cell types and secrete proteins that facilitate immune regulation, angiogenesis, revascularization, cutaneous wound healing, and tissue regeneration [2]. Despite the immense promise that ASCs

Abbreviations: SVF, stromal vascular fraction; ASCs, adipose-derived stem cells; eSVF, enzymatically isolated SVF; mSVF, mechanically isolated SVF.

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hold in regenerative medicine, their application is impeded by several challenges. For instance, ASCs exhibit poor survival following cryopreservation and thawing of lipoaspirates, difficulties in ex-vivo expansion, and a low retention rate after transplantation. Furthermore, isolating ASCs alone disrupts the stem cell niche, known as the microenvironment, which surrounds the stem cell, thereby adversely impacting their physiological function [3]. ASCs are predominantly located in the perivascular region of the stroma. As such, researchers have extracted SVF from adipose tissue for use in clinical applications. SVF is acquired as part of the aqueous fraction of lipoaspirate, containing a combination of pericytes, endothelial precursors (including endothelial progenitor cells and hemopoietic stem cells), immune cells, fibroblasts, and stromal/stem cells [4]. The two primary methods for separating SVF are enzymatic isolation and mechanical isolation. Enzymatic isolation involves the use of collagenase and other exogenous substances. This method, referred to as enzymatically isolated SVF (eSVF), is deemed to be more than "minimally manipulated" by the U.S. Food and Drug Administration [5]. Furthermore, this process is costly, time-consuming, and necessitates specialized infrastructure, such as a cleanroom facility, specialized equipment, reagents, and technical abilities. As a result, many approaches to mechanically isolating SVF have been established. These techniques are much easier and less complicated than those employing enzymes. Furthermore, mechanical approaches enable the isolation of SVF cells that possess stemness and immunosuppressive characteristics, which are comparable to those obtained via enzymatic digestion [6]. The domain of physical conditioning methodologies and their corresponding commercial apparatus is vast and varied, comprising advancements such as Lipogems, Lipocube Nano, and Hy-Tissue SVF. However, unlike enzymatic methodologies, established standards for mechanical methods are presently lacking. The present review aims to critically appraise mechanically isolated SVF (mSVF) and the various techniques employed to achieve mSVF from lipoaspirates. Additionally, a comprehensive discussion of the respective advantages and disadvantages of each methodology will be provided (see Fig. 1).

2. Mechanical isolation of SVF

Enzymatic isolation involves the utilization of collagenase to hydrolyze the intermolecular bonds within adipose tissue, allowing for the separation of stromal cells via centrifugation. The resultant end product is consistently in a liquid state. By contrast, the maintenance of the extracellular matrix and intercellular bonds within the mSVF is conserved. The ultimate outcome of this process is almost invariably in a solid form. Mechanical measures are utilized to ensure the extracellular matrix (ECM) and stromal cells. In light of this, Copcu et al. have suggested that the nomenclature "total stromal cells" is the most fitting definition [7]. Distinguished products include ECM/SVF-gel developed by Yao et al., lipoconcentrate, RE-fat, and stromal cell aggregates [8]. The aforementioned items possess a solid composition and have consequently been employed for volumetric augmentation of tissues, encompassing both contouring and facial augmentation [9–12]. Enzymatic breakdown of adipose tissue produces a singular-cell suspension, which leads to the obliteration of all intercellular interactions and the digestion of the ECM. In the aftermath of mechanical isolation, adipocytes are partly demolished, albeit intracellular and cell-ECM junctions remain unimpaired [13]. The ECM plays a pivotal role as a reservoir of growth factors and an instructional scaffold during the process of tissue regeneration. The presence of ECM is crucial for the optimal functioning of ASCs. Normally, mSVF is harvested through mechanical force, which ensures the preservation of ECM. Nonetheless, cell populations obtained by mechanical methods exhibit a higher prevalence of peripheral blood mononuclear cells and a considerably lower quantity of progenitor cells than those obtained via enzymatic methods [14]. ASCs exhibit a high concentration within the small and medium-sized vascular structures of adipose tissue, thereby leading to the retention of numerous progenitor cells within the vascular endothelial layers and connective tissue fragments of the lipoaspirate, without the need for enzymatic degradation of the collagen-based ECM. In a study conducted by Chaput et al., two mechanical procedures, namely, intensive vortexing/centrifugation and dissociation by intersyringe processing, were compared with collagenase digestion [15]. The study revealed that mSVF obtained through two distinct methods exhibit similar stemness and immunosuppressive properties to those of the eSVF. In addition, intersyringe processing demonstrated advantages over vortexing/centrifugation with respect to technical execution, cellular expansion, and clonogenic enrichment. However, the utilization of mechanical methods presents a major limitation, as excessive blunt pressure leads to decreased cell viability and a reduced number of stromal cells [13]. As such, researchers advocate for the collection of mSVF through the use of sharp blades to avoid excessive blunt pressure [16]. In support of this notion, Mashiko and colleagues compared two methods, namely squeeze and emulsification, and reported that squeeze of tissues may be less detrimental to cellular components compared to emulsification [13].

3. Basic physical methods

3.1. Centrifugation

Centrifugation is a widely utilized method for fat processing, which involves the separation of undesired constituents such as oil, blood, local anesthetic, and noncellular materials from lipoaspirate. The final density of adipose tissue, the number of progenitor cells, cell viability, and removal of contaminants are all closely associated with the speed of centrifugation, which is typically expressed in revolutions per minute (rpm) or acceleration in terms of gravitational force (g). Prantl et al. have demonstrated that the centrifugation of lipoaspirate results in a 1.3-fold increase in the stem cell yield per milliliter of the processed sample [17]. The utilization of centrifugation in the processing of adipose tissue for the isolation of mSVF has raised concerns regarding the possible detrimental effects of centrifugal forces on the cellular integrity and density of each cell type. However, previous studies have indicated that adipocyte populations can be effectively reduced while maintaining viable ASCs through centrifugation at appropriate forces (<3000 g), and that the number of viable SVF cells is unaffected even at higher centrifugal forces (up to 4200 g) [18]. Various techniques have been developed to further concentrate SVF cells, including washing, shaking/vibrating, and subsequent centrifugation. Cell-assisted lipotransfer, which involves the injection of autologous ASCs in conjunction with lipoaspirate, has been shown to enhance the long-term persistence of fat grafts. As such, point-of-care devices have been developed to isolate SVF and produce SVF-enhanced fat grafts using standardized and safe protocols. In summary, centrifugation is widely regarded as a safe and effective method for the processing of adipose tissue with minimal impact on cellular.

3.2. Washing/filtration

The primary objective of washing and filtration procedures is to eliminate any potential sources of contamination, such as nonviable components, debris, and oil, while also maximizing the

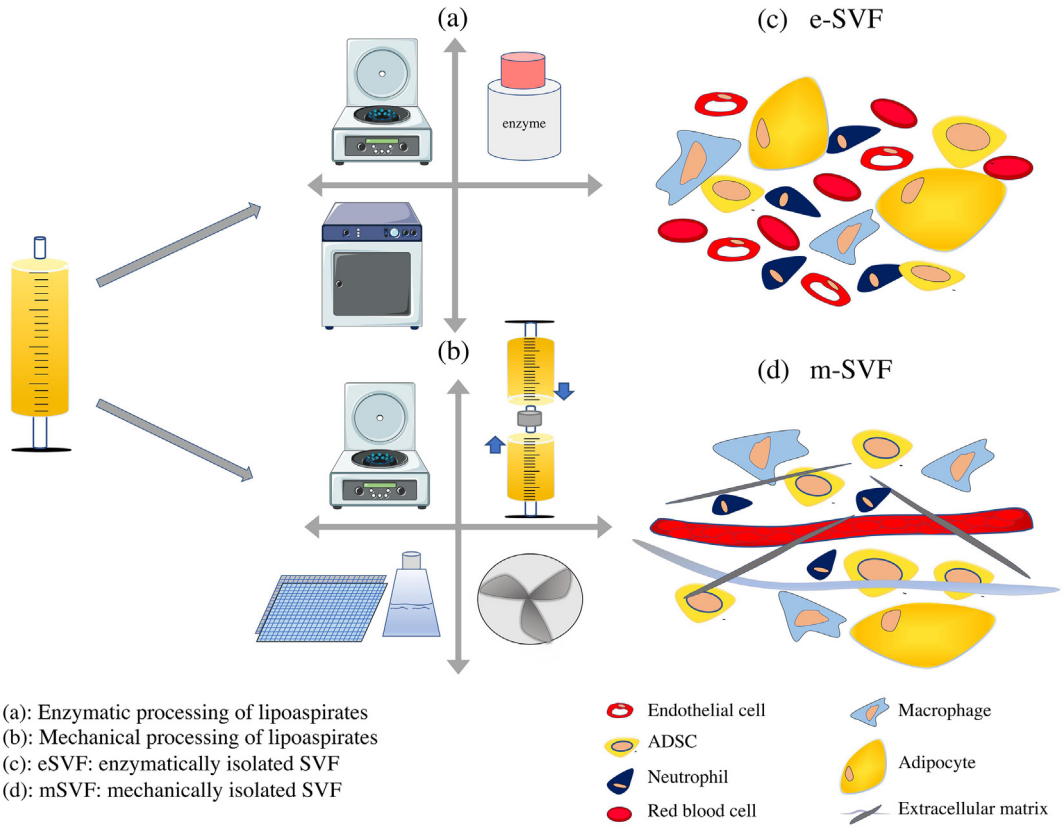

Fig. 1. Overview of SVF isolation techniques and comparison of the composition differences between eSVF and mSVF.

concentration of viable ASCs and other SVF cells. Commercial products, including Hy-Tissue SVF, Lipogems, FATStem systems, and MyStem system, employ washing and filtration techniques to purify adipose tissue [19–21]. The inclusion of oil components and cellular fragments in the final product can trigger a severe inflammatory response, thereby disrupting the desired therapeutic effect. However, a mild inflammatory response can promote adipose tissue regeneration, and excessive liquid content in the washed and filtered product can reduce its volumizing effect after transplantation. Filtering is often necessary for products that have undergone physical manipulation to remove larger tissue fragments that may impede clinical injection or block the needle used for administration.

3.3. Emulsification

In 2013, Tonnard et al. introduced a novel technique during liposuction aimed at facilitating fat processing and injection, which involves the transfer of fat between two 10 cc syringes connected by a female-to-female Luer-Lok connector. This process, referred to as emulsification, results in the production of a final product known as nanofat [3]. Emulsification is achieved by subjecting mature adipocytes to shear forces, leading to the release of the contents of their lipid droplets. Centrifugation of nanofat has been shown to increase the number of ASCs in the remaining fat tissue after removal of the oil phase. Numerous studies have been conducted to investigate the effects of emulsification on the composition and function of lipoaspirates (Table 1). Banyard et al. found that mechanical shear forces can up-regulate multipotency and pluripotency markers related to the regenerative capacity, suggesting that products obtained using shear force treatment might have a better regenerative effect [22]. However, two studies have revealed that the narrow Luer connector utilized in the transfer of fat between syringes generates higher shear forces, leading to increased damage of SVF cells and possibly affecting the proliferation of ASCs [23,24]. The beneficial effects of growth factors and cytokines secreted by ASCs have been repeatedly demonstrated, with studies showing that emulsification does not significantly alter the secretome composition of lipoaspirates [17]. Osinga et al. found that changing the number of times (0, 5, and 30) fat was shifted between syringes did not affect the cell number, cell viability, number of lipid droplets, vascular architecture, or ratio of cell types [25]. The utilization of a connector and filter system combination, as pioneered by Cohen in his development of the Lipocube, has gained widespread popularity. Through experimentation, it has been observed that implementation of the Lipocube Nano results in an impressive cell count of 2,240,000 cells per cubic centimeter, with a corresponding cell viability rate of 96.75% [26]. In general, by allowing a reduction in shuffling times or increasing the diameter of the Luer connector, emulsification can also reduce shear force. The final product typically contains both mature adipocytes and SVF cells, with some intact adipose tissue remaining after exposure to weak blunt force, which can be used for soft tissue augmentation. Emulsification has become a crucial step in the preparation of fat products, including mSVF and concentrated ASCs products, and has been shown to increase the density of ASCs and ECM by reducing the volume of oil [27].

3.4. Vibration

In 2014, Raposio et al. proposed a novel approach to homogenize fat through the use of vibration [6]. This method was carried out in a vibrating shaker, whereby samples were subjected to 3200 vibrations per minute for 6 min, followed by centrifugation at 558*g*

Table 1
Summary and main conclusions of emulsification process studies.

Author	Year	Main conclusions	Reference
Ye et al.	2021	Emulsification could increase the pluripotency of adipocytes. The viscosity of fat was directly proportional to the shear force applied. Emulsification did not affect the total number of cells, but significantly decreased the number of living cells.	[28]
Banyard et al.	2016	Emulsification did not affect the cell number; however, viability was greatly reduced compared with the stromal vascular fraction of standard lipoaspirate. Emulsification resulted in a stromal vascular fraction with higher proportions of endothelial progenitor cells, mesenchymal stem cells, and multilineage-differentiating stress-enduring cells. Mechanical shear stress increased the number of cells with progenitor phenotypes consistent with upregulation of multipotency and pluripotency markers.	[29]
Prantl et al.	2020	Emulsification led to a significant 2.6 ± 1.75-fold enrichment of adipose-derived stem cells attributable to volume reduction without reducing the viability of stem cells. The protein composition of the secretome did not change significantly after tissue homogenization.	[17]
Chen et al.	2020	Use of a Luer-Lok connector with a smaller diameter generated greater mechanical shear force, which lysed more fat cells during emulsification, thereby reducing the viability of adipose-derived stem cells in the stromal vascular fraction. Nanofat obtained using a 2 mm Luer-Lok connector had a better effect on skin rejuvenation than that generated using 1.5and 1.1 mm connectors.	[23]
Qiu et al.	2021	The smaller the aperture of the converter, the greater the mechanical force adipose tissue was exposed to during mechanical emulsification. Emulsification using converters with different apertures exerted different effects on the adipose tissue structure, cell content, and multipotency, but not on viability.	[24]
Osinga et al.	2015	The mechanical procedure of shifting lipoaspirated fat did not alter tissue viability or its microscopic structure. The number of shifts (0, 5, and 30) did not affect the cell number, viability, number of lipid droplets, vascular architecture, or ratio of cell types.	[25]

for an additional 6 min. The results showed a high yield of ASCs at 5 ± 1 × 105/80 mL. This technique generated less blunt pressure in comparison to emulsification and resulted in minimal damage to both adipocytes and SVF cells. The automated process was completed within 15 min. Lipogems, on the other hand, employs the use of small steel balls to achieve vibrating homogenization, thus maintaining the integrity of the stromal vascular architecture and resulting in a high yield of pericytes/ASCs with minimal mechanical force [20,21,30]. The mature adipocytes are preserved, with most products containing a high proportion of these cells.

3.5. Mincing/adinizing

The process of mincing or adinizing adipose tissue involves the use of a sharp blade to cut it to the desired dimensions. It has been suggested by scholars that blunt force generated during emulsification can cause significant damage to adipocytes and SVF cells, whereas sharp cutting using a razor blade is considered a gentler method for fat processing. The resulting products of this process are typically squeezed fat and AER-fat [13,16]. As cutting with sharp force does not drastically break down adipocytes, the end product typically contains a greater number of viable adipocytes, making it suitable for fat transplantation. Tiryaki et al. utilized three different blade grids on three Luer lock ports on a rotating canal to generate lipoaspirate, which, after centrifugation, yielded comparable mSVF and eSVF in terms of stromal cell composition and viability [31]. In a recent study [32], Copcu and Oztan introduced a novel system, named Adinizer, that employs sharp blades to cut ligaments and bonds within adipose tissue without inducing excessive blunt pressure. The Adinizer system was found to effectively free stromal cells in adipose tissue, facilitating adipose tissue transfer (ARAT) technique to obtain desired size fat grafts ranging from 4000- to 200-μm diameters. These grafts were then applied at varying depths to different aesthetic units of the face, and a guide was developed. Moreover, the authors utilized Mechanical stromal cell transfer (MEST) to obtain stromal cells from 100 mL of condensed fat using different indication-based protocols. The obtained cells showed a mean viability of 93% and cell counts ranging from 28.66 to 88.88 × 106. Importantly, the use of sharp blades in Copcu and Oztan's study helped preserve the structure of adipocytes, as evidenced by histopathological analysis revealing the presence of intact, viable adipocytes. This phenomenon is thought to be due to the effect of the sharp blade system employed. Notably, even after centrifugation, intact adipose tissue was still present and utilized for soft tissue augmentation.

4. Discussion

The utilization of mSVF in regenerative medicine exhibits multiple benefits over the usage of eSVF in various clinical applications. Research has indicated that single cells migrate within 24 h following injection [33]. The ECM, encompassing a microvascular network, serves as a natural scaffold for cells such as ASCs, and most likely enhances rapid vascularization and reperfusion. This is expected to amplify cell retention rates and augment clinical outcomes. In situations involving early scar formation, wound healing, or organ fibrosis, mSVF is considered to be a more suitable therapeutic approach, requiring non-enzymatic isolation procedures. Conversely, when excessive pre-existing scar formation exists, the ECM in SVF may not be appropriate, and therefore eSVF application may be more appropriate.

However, when selecting the optimal mSVF product for transplantation, several factors need to be considered, including the preparation time, the number and viability of ASCs, the complexity of the procedure, and the different clinical needs. The yield and viability of SVF cells, obtained through mechanical methods, vary significantly among donors depending on their age, harvest location, and co-morbidities such as obesity [34,35]. Therefore, there is substantial variation in cell yield, cell viability, and the composition of SVF when different mechanical isolation procedures are compared [Table 2]. In general, eSVF results in a higher cell viability of ASCs as compared to mSVF. The latter causes varying degrees of damage to ASCs due to mechanical force. A comparison of several methods has revealed that vibration and mincing/adinizing techniques cause less severe damage to ASCs, while emulsification exerts a relatively large blunt shear force effect and causes more damage. However, the degree of damage can be modulated by adjusting the diameter of the Luer connector or the number of shuffling times. Osinga et al. [25] found that the viability of ASCs was not significantly changed by shuffling times below 30. In addition to the damage to ASCs, there is also a large degree of damage to adipocytes. Adipose tissue is fragile, and adipocytes are susceptible to shear force, with the extent of damage dependent on their size. Emulsification may selectively destroy fragile, mature, and large adipocytes, and with subsequent

Table 2
Summary of Studies on Mechanical Preparation of mSVF and their Effects on Viability and Production of ASCs.

Author	Method	Products or procedure	ASCs content (number or percentage of SVF population)	Viability	Number of free nucleated cells	Reference
Tiryaki et al.	Mincing, filtration, and centrifugation	3-step mechanical digestion method	2.82×10^4/mL	85.86% ± 5.74%	1.34×10^6/mL	[31]
Baptista et al.	Red blood cell lysis and centrifugation	MPLA	$1.2 \pm 0.37 \times 10^4$/mL	/	$24.0 \pm 7.4 \times 10^4$/mL	[40]
Raposio et al.	Vibration and centrifugation	adipose-derived stem cell novel and standard isolation technique	$5 \pm 1 \times 10^5$/80 mL	/	1×10^7/80 mL	[6]
Mashiko et al.	Centrifugation, filtration, emulsification, and squeezing	SQ-fat	SQ-fat: 1.5×10^5/ml	SQ-fat: 89.9% ± 4.6%	/	[13]
		Re-fat	Re-fat: 1.4×10^5/ml	Re-fat: 90.6% ± 2.8%	/	
		FEF	/	FEF:39.3 ± 9.1%	/	
Yao et al.	Centrifugation and emulsification	SVF/ECM-gel	$1.9 \pm 0.2 \times 10^5$/mL	/	$4.1 \pm 0.3 \times 10^5$/mL	[36]
Tonnard et al.	Emulsification and filtration	nanofat	0.1×10^4/mL	/	1.975×10^4/mL	[1]
Pallua et al.	Emulsification and centrifugation	lipoconcentrate	$2.29 \pm 0.21 \times 10^5$/g	/	$10.45 \pm 0.71 \times 10^5$/g	[41]
Fan et al.	Filtration and mincing	AER fat	/	/	$6.0 \pm 1.10 \times 10^4$/mL	[37]
Chaput et al.	Vortexing/centrifugation and emulsification	Dis	/	Dis: 45.53% ± 3.49%	/	[15]
		V/C	/	V/C: 54.53% ± 7.55%	/	
Copcu et al.	Adinizing and centrifugation	MEST	/	93.00%	$28.66–88.88 \times 10^6$/100 mL	[32]
Van Dongen et al.	Centrifugation and emulsification	FAT	/	/	$2.7 \pm 1.1 \times 10^6$/ml	[27]
Bianchi et al.	Vibration, washing and filtration	Lipogems Product	/	100.00%	/	[20]
Cohen et al.	Emulsification and filtration	Lipocube Nano	37.29%	96.05%	2.24×10^6/ml	[26]
Sesé et al.	Emulsification and washing	nanofat	/	76.80%	$6.63 \pm 0.47 \times 10^6$/g	[42]

MPLA: mechanically processed lipoaspirate adipose tissue.
SQ-fat: squeezed fat; Re-fat: residual tissue of emulsified fat.
AER-fat: adipose-derived progenitor cell enrichment fat.
FEF: filtrated fluid of emulsified fat.
Dis: dissociation by intersyringe processing; V/C: intensive vortexing/centrifugation method.
MEST: mechanical stromal cell transfer; FAT: fractionation of adipose tissue procedure.

centrifugation to remove excess oil, the volume of the final product can be greatly reduced to achieve a high concentration of ASCs and ECM of mSVF products, a feature not available in other mechanical methods. Such as SVF-gel [36], where the final volume is only 1/10 of the initial state, and the concentration of ASCs increased several times than Coleman fat. Another advantage of emulsification is that the resulting product can be injected through a small (27 G) needle, which is necessary for clinical applications requiring only small volume and fine-tuned injections, such as the treatment of chronic arthritis, wound healing and facial augmentation [9,10]. On the contrary, methods for preparing mSVF that do not inflict significant damage to adipocytes, such as vibration or mincing, are preferred for large tissue volumization. Compared to traditional fat grafts, mSVF has several advantages, including higher concentration of SVF cells and better retention rates upon fat transplantation. When transplanted into mice it was found that the structure of adipose tissue under a light microscope appears more uniform, with fewer oil cysts [37]. The utilization of mSVF has demonstrated a capacity to consistently sustain the volume of adipose grafts. The augmented quantity of ECM within the graft may account for its relatively constant post-transplant volume. To evaluate the intricacy of diverse mSVF preparation techniques and the resulting ASCs content, a comparative analysis was conducted [Table 2]. Nevertheless, determining the superiority of any particular method is challenging, and further research is warranted to identify the optimal preparation approach for mSVF. Leaving fat aspitation in vitro for too long can result in cell necrosis. Considering the time constraints in clinical settings, the preparation time for mSVF should not be excessively prolonged. The current trend in preparing mSVF products is to combine several basic physical methods to achieve simplicity, short processing time, and high efficiency. For instance, the Solodeev team recently developed a closed, integrated, fully automated mSVF extraction device that integrates washing, filtration, and cutting processes in just 15 min, without the need for additional processing [38]. Furthermore, innovative techniques, like microfluidics technology, have emerged. Microfluidics technology is a precision method for controlling and manipulating fluids at the microscale. The Lee team employed a microfluidic sorter cascade—a system of microfluidic devices—to effectively separate and enrich ASCs from other cell types in fat tissue [39]. This approach demonstrated an impressive efficiency of more than 90% in cell separation based on their size. The recent publication by Ghiasloo et al. [39]constitutes the most comprehensive investigation into the clinical applications of mechanically obtained stromal cells. In their study, the authors conducted a comprehensive scan of 4505 articles and compiled a database of 1458 diseases. Notably, the authors identified ten distinct modifications of the nanofat concept for obtaining stromal cells through mechanical means. The findings of this study are

particularly noteworthy given the extensive body of research that has been conducted on the topic.

5. Conclusion

The mSVF exhibits a vast range of prospective applications in the fields of volume filling and stem cell therapy. It is distinguished by its swift and enzyme-free preparation, sans the use of exogenous reagents. Each distinct preparation method presents its unique benefits and limitations, thereby necessitating a critical assessment of indications to determine the optimal preparation method. Consequently, there is a pressing need for comparative investigations to establish the most efficacious mechanical preparation approach.

Conflicts of interest

All authors declare that they have no conflicts of interest to disclose.

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