Orthopaedics & Traumatology: Surgery & Research 103 (2017) 927–932

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review article

Use of adipose tissue and stromal vascular fraction in hand surgery

I. Nseir[a,*], F. Delaunay[a], C. Latrobe[b], A. Bonmarchand[a], D. Coquerel-Beghin[a], I. Auquit-Auckbur[a]

[a] Service de chirurgie plastique et chirurgie de la main, CHU de Rouen, 1, rue de Germont, 76000 Rouen, France
[b] Service de chirurgie orthopédique et traumatologique, CHU de Rouen, 1, rue de Germont, 76000 Rouen, France

ARTICLE INFO

Article history:
Received 30 August 2016
Accepted 11 May 2017

Keywords:
Lipofilling
Stromal vascular fraction
Adipose-derived stem cells
Dupuytren's contracture
Systemic sclerosis
Hand

ABSTRACT

Adipose tissue is an abundant source of various cell types including not only adipocytes, but also progenitor and endothelial cells from thestroma. Interest in adipose tissue has surged since the identification in 2001 of adipose-derived stem cells (ADSCs) and of the stromal vascular fraction (SVF) obtained from adipose tissue by enzymatic digestion and centrifugation. SVF has been proven effective in ensuring tissue regeneration, thus improving tissue trophicityand vascularisation. These effects have generated strong interest among both physicians and surgeons, particularly in the field of hand surgery. Several applications have been developed and used, for instance to treat Dupuytren's contracture, systemic sclerosis-related hand lesions, and skin ageing at the hand. Other uses are being evaluated in clinical or animal studies. The objective of this article is to review the capabilities of adipose tissue and their current and potential applications in hand surgery.

1. Introduction

Adipose tissue is an abundant source of various cell types. Being derived from the mesenchyme, it contains not only adipocytes (well differentiated cells that cannot divide [1]), but also progenitor and endothelial cells from the stroma. Adipose tissue is an endocrine organ that releases numerous adipokines capable of acting as both autocrine and paracrine factors [2,3]. Adipose tissue is renewed constantly at a rate of about 10% per year [4] thanks to the presence of progenitor cells that can undergo differentiation. These progenitor cells have been designated adipose-derived stem/stromal cells (ADSCs) by the International Federation for Adipose Therapeutics and Science (IFATS). They are found within a larger component known as the stromal vascular fraction (SVF).

SVF has demonstrated therapeutic efficacy in many domains including tissue regeneration, with improvements in tissue trophicity and vascularisation. These advantages are generating considerable interest among physicians and surgeons. More specifically, in the field of hand surgery, the broad array of disorders, injuries, and tissues involved, together with the major functional importance of the hand, have provided a strong impetus to the development of new treatments based on the regenerative capabilities of adipose tissue. Among these new techniques and applications, which cover a vast spectrum, some have been validated and are widely used, whereas others are still being developed or evaluated in animal studies.

The objective of this work is to review the capabilities of adipose tissue and their current and potential applications in hand surgery.

2. Adipose tissue transfer techniques

Many methods have been developed to allow the use of adipose tissue as a filler and volume enhancer. In the 1970s, Illouz developed liposuction, using a cannula to aspirate the fat, which was then re-injected at other sites as a filler [5–7]. Subsequently, Coleman coined the term 'lipostructure' to designate a filling method based on careful attention to the fragile nature of adipose tissue [8,9]. Several steps are required to harvest adipose tissue. The preferred donor sites are the abdomen, trochanters, and medial aspect of the knees [10]. A solution is usually injected into the donor site to allow hydro-dissection and diminish tissue trauma. Injectable saline is used, with or without a local anaesthetic (e.g., lidocaine or ropivacaine) and/or a vasoconstricting agent (e.g., adrenalin).

Atraumatic liposuction is applied to harvest the fat. Studies have established that manual syringe aspiration at pressureslower than -1.0/–0.5 bar substantially decreases adipocyte damage [11,12] (Fig. 1A). Many features of the suction cannulas can affect

* Corresponding author.
E-mail addresses: nseir.iad@gmail.com (I. Nseir), flore.delaunay@yahoo.fr (F. Delaunay), ch.latrobe@gmail.com (C. Latrobe), albanebonmarchand@yahoo.fr (A. Bonmarchand), doro_coquerel@hotmail.com (D. Coquerel-Beghin), isabelle.Auquit@chu-rouen.fr (I. Auquit-Auckbur).

http://dx.doi.org/10.1016/j.otsr.2017.05.017
1877-0568/

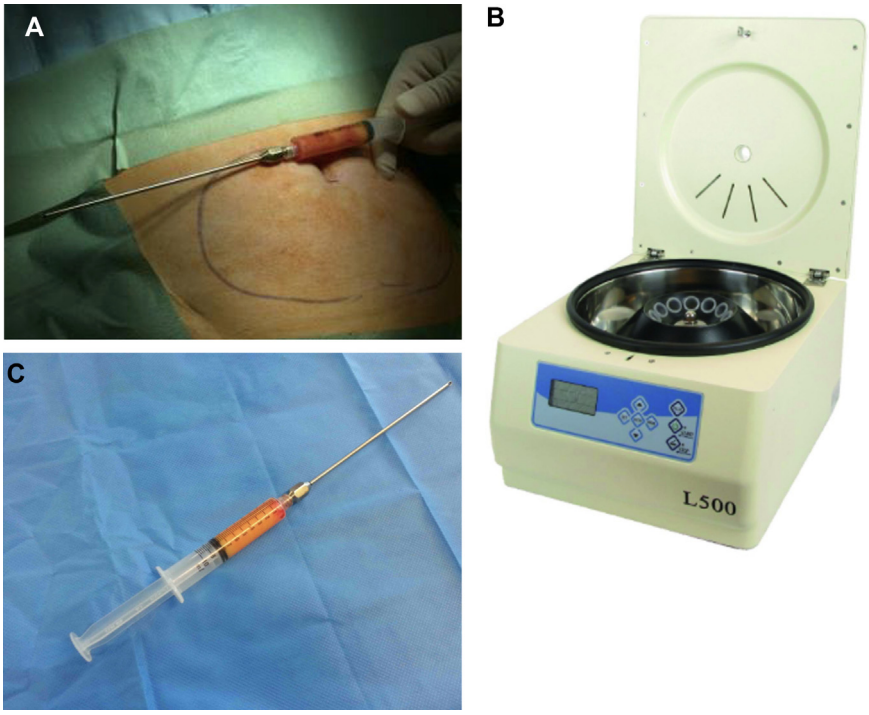

Fig. 1. A–C. Harvesting and injection of adipose tissue.

graft quality (e.g., diameter, size, and number and orientation of the holes). To date, no cannula model has been proven superior over the others. The harvested fat is washed with saline then centrifuged (Fig. 1B) to purify the graft while maximising adipocyte survival. The best compromise may be centrifugation at 3000 rpm for 3 minutes [13–15]. Closed circuit systems are available for these steps to decrease graft oxidation and cell necrosis [16].

At the recipient site, retrograde injection is used to avoid intravascular injection of the fat tissue. The lipostructure technique developed by Coleman relied on a 17-gauge injection cannula (Fig. 1C), which may not be appropriate for all recipient sites, such as the inelastic tissues of the hand and face affected with systemic sclerosis. Micro-injections can be performed using 20-, 23-, or even 25-gauge cannulas without damaging the adipocytes [17].

3. Technique for extracting the stromal vascular fraction (SVF) and adipose-derived stem cells (ADSCs)

SVF is the cell pellet obtained after washing, enzymatic digestion, and centrifugation of fat harvested by liposuction. It contains many cell populations including pre-adipocytes, endothelial and pre-endothelial cells (10% to 20%), mesenchymal cells (ADSCs, 15% to 30%), pericytes (3% to 5%), leukocytes and macrophages (25% to 45%), and fibroblasts (capable of producing collagen and organising an extra-cellular matrix) [18–21].

Extraction of SVF involves several steps: washing with phosphate buffer saline to remove cellular debris, digestion bycollagenasesat 37 °C to release the cell mixture embedded in the extra-cellular matrix between the adipocytes, and centrifugation to separate the SVFfrom the digestion buffer and adipocytes (1500 rpm for 5 minutes). This entire procedure can be automated and standardised by using devices such as the Celution® system (Cytori®, San Diego, CA, USA), which requires about 2 hours [22].

French legislation requires that SVF extraction, even when automated, be performed in a cell therapy laboratory accredited by the PPMI.[1] The nanofat grafting technique described recently by Tonnard et al. is a mechanical SVF extraction technique that can be used in the operating room. The fat tissue is transferred rapidly from one syringe to another to break down the extracellular matrix and extract the SVF. Nanofat is used chiefly for the regenerative effects of SVF rather than as a filler (given the small volumes) [23,24] and may therefore be particularly well suited to hand surgery. Importantly, despite their practical advantages, these SVF extraction techniques have lower ADSC yields compared to conventional enzymatic digestion followed by cell culture.

ADSCs can be isolated from SVF, cultured in vitro, and used for cell therapy. Advantages of ADSCs include ease of collection and isolation and abundance in the body. Since they were first characterised by Zuk et al. in 2001 [25], ADSCs have generated considerable research interest, due to their multipotency. The adipose tissue is estimated to contain about 2% of mesenchymal stem cells (MSCs), compared to only 0002% in the bone marrow (bone marrow MSCs, BM-MSCs) [26].

French law classifies SVF among the innovative therapeutic drugs, which are strictly regulated. For instance, only accredited cell therapy laboratories can produce SVF, and the product must be subjected to cellular and microbiological tests at regular intervals. Adipose tissue transfer and nanofat grafting are not classified as innovative therapeutic drugs and, consequently, sample preparation and re-injection can be performed in the operating room.

These treatments have been expanding rapidly in recent years, in many fields [27]. SVF and ADSCs have been shown to stimulate angiogenesis [28] more effectively than MB-MSCs [29] and to improve the trophicity and repair of damaged tissues (e.g., skin burns [30,31], radiodermatitis [32], and myocardial infarcts [33–35]). SVF and ADSCs also exert immunomodulating effects [15,36,37] and exhibit considerable differentiation potential [38]. Thus, in vitro, ADSCs can be used to obtain myoblasts, osteoblasts,

[1] *Plate-forme de production de médicaments de thérapie innovante* (Production Platform for Innovative Medications).

and chondrocytes [39]. These many capabilities of ADSCs and SVF have also been used over the last few years to develop new treatments for the different domains of hand surgery.

4. Dupuytren's contracture

Dupuytren's contracture is defined as non-malignant chronic fibromatosis of the superficial palmar fascia. At present, fasciectomy or dermofasciectomy is the standard treatment. The recurrence rate varies from 10% to 40%. Less invasive treatment options have been developed, such as needle aponeurotomy. However, needle aponeurotomy has a high recurrence rate of 50% to 60% after 4 years [40,41]. More recent methods include local collagenase injections, for which longer term follow-up data for large cohorts are still needed. In addition, collagenase injections can exacerbate the inflammatory reaction and cause tendon damage [42,43].

In animal models, MSCs seem to play a major role in diminishing fibrosis of the lungs, liver, kidneys, heart; as well as fibrosis of the penis in a model of Peyronie's disease [44–46]. MSCs have also been shown to modulate immune and inflammatory responses [47].

Dupuytren's contracture is characterised by excessive myofibroblast proliferation [48]. In vitro, ADSCs, acting via both direct contact and the release of multiple factors, inhibited the proliferation and contractility of Dupuytren myofibroblasts and also decreased the expression of alpha-smooth muscle actin protein, whereas BM-MSCs tended to increase the contractility of Dupuytren myofibroblasts [49]. In 2011, R. Khouri described a new treatment option consisting in extensive superficial (2–3 mm) percutaneous aponeurotomy from proximal to distal along the cord, followed by the transfer of autologous adipose tissue [50]. In patients with various Tubiana stages of Dupuytren's contracture, this technique diminished the flexion contractures, from 61° to 27° at the proximal interphalangeal joint and from 37° to -5° at the metacarpophalangeal joint. No major complications occurred. Time to function recovery was 7–10 days and skin trophicity improved over the treated sites [50]. These results indicate that adipose tissue and SVF hold promise for the treatment of Dupuytren's contracture. Ongoing studies are evaluating this technique to determine the efficacy and recurrence rate comparatively to currently used techniques.

5. Systemic sclerosis

Systemic sclerosis is a rare auto-immune disease in which microvascular damage results in fibrosis of the skin and subcutaneous tissue. Involvement of the hands is a nearly consistent feature that substantially impairs quality of life [51]. Disability due to the hand lesions accounts for 75% of the overall disability from systemic sclerosis [52]. The main sources of disability are Raynaud's phenomenon, acrocyanosis, ischaemic and traumatic digital ulcers, subcutaneous calcinosis, and fibrosis of the skin. Improving hand function is a major treatment objective in patients with systemic sclerosis.

The regenerative, anti-inflammatory, immuno-modulating, and pro-angiogenic effects of SVF and ADSCs have been put to use in recent years for the treatment of systemic sclerosis lesions, notably at the fingers. In a mouse model of systemic sclerosis induced by repeated bleomycin injections, subcutaneous injections of fat and SVF significantly decreased dermal fibrosis and increased local vascularisation [53].

A recent study assessed autologous fat grafting in 21 hands of 13 patients with Raynaud's phenomenon (secondary in 11 patients and primary in 2 patients) [54]. The effects included significant pain relief and decreases in the number, duration, and severity of cold attacks. Del Papa et al. recently reported good outcomes after SVF injection to treat digital ulcers in patients with systemic sclerosis [55]. The ulcers healed within a mean of 4 weeks; the pain was reduced; and capillaroscopy after 1, 3, and 6 months showed a significant increase in the number of capillaries [55].

SCLERADEC (#NCT01813279) evaluated digital SVF injections in 12 patients with systemic sclerosis [56], in 2013, under the direction of Prof. Magalon. SVF was injected subcutaneously, in contact with the neuro-vascular pedicles. The treatment proved safe and significantly improved the hand function scores (Cochin Hand Function Scale, Raynaud Condition Score, and Scleroderma Health Assessment Questionnaire) at the 6-month study-completion visit and at re-evaluation after 1 year [57].

Although these studies have limited statistical power, they support the usefulness of adipose tissue and SVF for the treatment of hand lesions due to systemic sclerosis. The results of other studies are expected soon. In particular, SCLERADEC II is a multicentre randomised placebo-controlled double-blind trial of the efficacy of injections of adipose tissue-derived SVF that is ongoing in France. Ten fingers of patients with systemic sclerosis will be included. The primary outcome is the Cochin Hand Function Scale score after 3 months comparatively to the control group.

6. Other applications

The spectrum of applications of adipose tissue-based treatments has expanded considerably, particularly since the identification of SVF and ADSCs. Many fields remain to be explored. More specifically, uses for the multipotency of ADSCsin the field of hand surgery remain to be discovered.

6.1. Bone regeneration

ADSCs can differentiate into osteoblasts and may therefore play a role in bone regeneration. SVF and ADSCs have been used in several patients to fill bony defects, with satisfactory outcomes [58,59]. In a pig model, ADSCs seemed to expedite bone healing not only when injected directly into the lesion, but also when administered systemically [60]. This treatment may constitute a less invasive alternative to bone grafting for bone reconstruction or the treatment of pseudarthrosis. It may also be useful as an adjunct to conventional grafting in the treatment of pseudarthrosis and arthrodesis non-union or of sites at high risk for impaired bone healing.

6.2. Cartilage regeneration

ADSCs have been reported to differentiate into chondroblasts in vitro and in vivo [61]. The ability of ADSCs to regenerate cartilage has been demonstrated in animal studies, in which adding ADSCs allowed the complete reconstruction of articular and extra-articular cartilage defects [62,63]. The management of sequelae, remodelling, and deformities related to degenerative or post-traumatic osteoarthritis is a major component of everyday hand surgery. In the future, these new options for achieving cartilage regeneration may be incorporated into the therapeutic armamentarium available to hand surgeons.

6.3. Nerve reconstruction

The potential of adipose tissue for achieving nerve injury repair is also generating interest among researchers. For the repair of major nerve injuries, autologous nerve grafting often results in donor site morbidity and sometimes produces disappointing outcomes. Studies in animals (particularly murine models) have established that ADSCs and SVF enhance nerve regeneration. Di Summa et al. reported enhanced nerve regrowth within fibrin

nerve conduitscontaining ADSCs or SVF compared to controls [64]. Uncultured SVF has also been found to markedly enhance nerve regeneration. Thus, Mohammadi et al. [65] observed a significant increase in sciatic nerve regeneration in vivo in rats treated with SVF compared to the controls. Benefits of SVF included enhanced functional recovery, a shorter time to recovery, and improved muscle trophicity. Immunohistochemistry showed higher numbers of Schwann cell-like cells in the SVF group, as well as an overall improvement in nerve trophicity, suggesting that the extracellular matrix components supplied by SVF contribute to improve Schwann cell proliferation and, therefore, axon regeneration. Finally, Papalia et al. reported that the use of whole adipose tissue for nerve gap repair slowed functional recovery, indicating that centrifugation and SVF isolation are indispensable [66]. These research efforts can be expected to result in promising innovations for achieving nerve suture and repair, which are common problems in hand surgery and microsurgery.

6.4. Angiogenesis

SVF and ADSCs have been proven to stimulate local angiogenesis and to correct ischaemia-related tissue disturbances by promoting neo-angiogenesis and diminishing local inflammatory responses. This tissue regeneration capability has been demonstrated in many studies and numerous fields including digital ulcers due to systemic sclerosis [67], healing of skin burns [32,33], trophicity of tissues exposed to radiation therapy, 36 spinal cord injury (viapituitary adenylate cyclase-activating polypeptide [PACAP]) [68], and myocardial regeneration at sites of infarction (after intramyocardial [69]or intravenous [70] injection). Thus, SVF may become a major tool for treating ischaemic disorders and enhancing the vascular supply to areas surrounding tissue defects, with the goal of increasing the success rate of coverage procedures.

6.5. Wound healing

SVF and ADSCs have been shown to improve skin healing in animal models. The addition of SVF increased local vascularisation and fibroblast activity [31,71]. When applied to hypertrophic scars, SVF significantly diminished the production of collagen and blunted the inflammatory response [72]. These effects were first demonstrated in animal models then used to correct facial scars due to burns or trauma [73]. SVF therapy improved not only cosmesis, but also skin trophicity and scar tissue pain. In another study, the injection of autologous fat into painful scars provided substantial pain relief and improved functional scores [74].

The use of adipose tissue to treat impaired wound healing and scar tissue pain may constitute an alternative to scar tissue excision.

6.6. Tendinopathies

ADSCs have also been tested for the treatment of tendinopathies. The injection of ADSCs improved the histological tendon lesions and normalised the collagen levels within injured tendons [75]. In rats, ADSC therapy significantly benefitted the treatment of experimentally induced rotator cuff tendinitis [76]. In 8 patients with lateral epicondylitis of the elbow, autologous fat injection around the epicondyle was effective in alleviating the pain [77].

These data suggest that SVF may have a role in the treatment of tendinitis. Currently available treatments remain disappointing, and tendinitis often results in chronic pain and major functional impairments.

6.7. Skin rejuvenation at the hand

Aging of the hands is due to subcutaneous tissue atrophy, impaired skin trophicity, and increased visibility of the dorsal veins, tendons, and bony prominences. The injection of small amounts of autologous fat can be used to rejuvenate the dorsal aspect of the hands. After centrifugation, 20 mL of fat is injected into each hand, using 1- to 3-mL syringes, into the subdermal plane, superficial to the dorsal veins [78,79].

7. Conclusion

Fat tissue has been a strong focus of scientific and therapeutic interest in recent years. There is a large reservoir of readily accessible fat tissue that may be used to create volume or, after isolation of SVF and ADSCs, to enhance trophicity. Many recent studies have demonstrated that adipose tissue exerts regenerative effects when used whole after centrifugation, after isolation of the SVF, or after in vitro cell culture in the laboratory. The hand can be affected by a broad array of lesions, whose treatment is likely to benefit from these new techniques.

Ongoing studies whose publication is expected in the near future will open up new treatment possibilities with concrete applications in many fields, some of which may be relevant to hand surgery.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Hausman DB, DiGirolamo M, Bartness TJ, Hausman GJ, Martin RJ. The biology of white adipocyte proliferation. Obes Rev 2001;2:239–54.
[2] Blüher M. Clinical relevance of adipokines. Diabetes Metab J 2012;36:317–27, http://dx.doi.org/10.4093/dmj.2012.36.5.317.
[3] Lehr S, Hartwig S, Sell H. Adipokines a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin Appl 2012;6:91–101, http://dx.doi.org/10.1002/prca.201100052.
[4] Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature 2008;453:783–7, http://dx.doi.org/10.1038/nature06902.
[5] Illouz YG. The fat cell "graft": a new technique to fill depressions. Plast Reconstr Surg 1986;78:122–3.
[6] Illouz YG. Present results of fat injection. Aesthetic Plast Surg 1988;12:175–81.
[7] Illouz YG. Adipoaspiration and "filling" in the face. Facial Plast Surg FPS 1992;8:59–71, http://dx.doi.org/10.1055/s-20081064631.
[8] Coleman SR. Facial recontouring with lipostructure. Clin Plast Surg 1997;24:347–67.
[9] Coleman SR. Structural fat grafts: the ideal filler? Clin Plast Surg 2001;28:111–9.
[10] Li K, Gao J, Zhang Z, Li J, Cha P, Liao Y, et al. Selection of donor site for fat grafting and cell isolation. Aesthetic Plast Surg 2013;37:153–8, http://dx.doi.org/10.1007/s00266-012-9991-1.
[11] Har-Shai Y, Lindenbaum ES, Gamliel-Lazarovich A, Beach D, Hirshowitz B. An integrated approach for increasing the survival of autologous fat grafts in the treatment of contour defects. Plast Reconstr Surg 1999;104:945–54.
[12] Jauffret JL, Champsaur P, Robaglia-Schlupp A, Andrac-Meyer L, Magalon G. Arguments in favor of adipocyte grafts with the S.R Coleman technique. Ann Chir Plast Esthet 2001;46:31–8.
[13] Coleman WP, Autologous fat transplantation. Plast Reconstr Surg 1991;88:736.
[14] Kurita M, Matsumoto D, Shigeura T, Sato K, Gonda K, Harii K, et al. Influences of centrifugation on cells and tissues in liposuction aspirates: optimized centrifugation for lipotransfer and cell isolation. Plast Reconstr Surg 2008;121, http://dx.doi.org/10.1097/01.prs.0000299384.53131.87 [1033–41; discussion 1042–3].
[15] Kim IH, Yang JD, Lee DG, Chung HY, Cho BC. Evaluation of centrifugation technique and effect of epinephrine on fat cell viability in autologous fat injection. Aesthetic Surg J Am Soc Aesthetic Plast Surg 2009;29:35–9, http://dx.doi.org/10.1016/j.asj.2008.09.004.
[16] Coleman SR. Long-term survival of fat transplants: controlled demonstrations. Aesthetic Plast Surg 1995;19:421–5.
[17] Nguyen PSA, Desouches C, Gay AM, Hautier A, Magalon G. Development of micro-injection as an innovative autologous fat graft technique: the use

of adipose tissue as dermal filler. J Plast Reconstr Aesthetic Surg JPRAS 2012;65:1692–9, http://dx.doi.org/10.1016/j.bjps.2012.06.014.
[18] Gimble J, Guilak F. Adipose-derived adult stem cells: isolation, characterization, and differentiation potential. Cytotherapy 2003;5:362–9, http://dx.doi.org/10.1080/14653240310003026.
[19] Dong Z, Peng Z, Chang Q, Lu F. The survival condition and immunoregulatory function of adipose stromal vascular fraction (SVF) in the early stage of nonvascularized adipose transplantation. PloS One 2013;8:e80364, http://dx.doi.org/10.1371/journal.pone.0080364.
[20] Bourin P, Bunnell BA, Casteilla L, Dominici M, Katz AJ, March KL, et al. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: a joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). Cytotherapy 2013;15:641–8, http://dx.doi.org/10.1016/j.jcyt.2013.02.006.
[21] Eto H, Ishimine H, Kinoshita K, Watanabe-Susaki K, Kato H, Doi K, et al. Characterization of human adipose tissue-resident hematopoietic cell populations reveals a novel macrophage subpopulation with CD34 expression and mesenchymal multipotency. Stem Cells Dev 2013;22:985–97, http://dx.doi.org/10.1089/scd.2012.0442.
[22] Fraser JK, Hicok KC, Shanahan R, Zhu M, Miller S, Arm DM. The Celution® system: automated processing of adipose-derived regenerative cells in a functionally closed system. Adv Wound Care 2014;3:38–45, http://dx.doi.org/10.1089/wound.2012.0408.
[23] Tonnard P, Verpaele A, Peeters G, Hamdi M, Cornelissen M, Declercq H. Nanofat grafting: basic research and clinical applications. Plast Reconstr Surg 2013;132:1017–26, http://dx.doi.org/10.1097/PRS.0b013e31829fe1b0.
[24] Stuzin JM, Discussion:. Nanofat grafting: basic research and clinical applications. Plast Reconstr Surg 2013;132:1027–8, http://dx.doi.org/10.1097/PRS.0b013e31829fe246.
[25] Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7:211–28, http://dx.doi.org/10.1089/107632701300062859.
[26] Wilson A, Butler PE, Seifalian AM. Adipose-derived stem cells for clinical applications: a review. Cell Prolif 2011;44:86–98, http://dx.doi.org/10.1111/j.1365-2184.2010.00736.x.
[27] Nguyen A, Guo J, Banyard DA, Fadavi D, Toranto JD, Wirth GA, et al. Stromal vascular fraction: a regenerative reality? Part 1: current concepts and review of the literature. J Plast Reconstr Aesthet Surg 2016;69:170–9, http://dx.doi.org/10.1016/j.bjps.2015.10.015.
[28] Planat-Benard V, Silvestre J-S, Cousin B, André M, Nibbelink M, Tamarat R, et al. Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. Circulation 2004;109:656–63 [10.1161/01.CIR.0000114522.38265.61].
[29] Rehman J, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation 2004;109:1292–8 [10.1161/01.CIR.0000121425.42966.F1].
[30] You H-J, Han S-K. Cell therapy for wound healing. J Korean Med Sci 2014;29:311, http://dx.doi.org/10.3346/jkms.2014.29.3.311.
[31] Atalay S, Coruh A, Deniz K. Stromal vascular fraction improves deep partial thickness burn wound healing. Burns Int Soc Burn Inj 2014;40:1375–83, http://dx.doi.org/10.1016/j.burns.2014.01.023.
[32] Rigotti G, Marchi A, Galiè M, Baroni G, Benati D, Krampera M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. Plast Reconstr Surg 2007;119:1409–22, http://dx.doi.org/10.1097/01.prs.0000256047.47909.71 [discussion 1423-4].
[33] Schenke-Layland K, Strem BM, Jordan MC, Deemedio MT, Hedrick MH, Roos KP, et al. Adipose tissue-derived cells improve cardiac function following myocardial infarction. J Surg Res 2009;153:217–23, http://dx.doi.org/10.1016/j.jss.2008.03.019.
[34] Valina C, Pinkernell K, Song Y-H, Bai X, Sadat S, Campeau RJ, et al. Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion and remodelling after acute myocardial infarction. Eur Heart J 2007;28:2667–77, http://dx.doi.org/10.1093/eurheartj/ehm426.
[35] Leblanc AJ, Nguyen QT, Touroo JS, Aird AL, Chang RC, Ng CK, et al. Adipose-derived cell construct stabilizes heart function and increases microvascular perfusion in an established infarct. Stem Cells Transl Med 2013;2:896–905, http://dx.doi.org/10.5966/sctm.2013-0046.
[36] Bertheuil N, Chaput B, Ménard C, Varin A, Garrido I, Grolleau JL, et al. Les cellules stromales mésenchymateuses du tissu adipeux: historique, isolement, propriétés immunomodulatrices et perspectives cliniques. Ann Chir Plast Esthet 2015;60:94–102, http://dx.doi.org/10.1016/j.anplas.2014.09.014.
[37] Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, et al. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. Br J Haematol 2005;129:118–29, http://dx.doi.org/10.1111/j.1365-2141.2005.05409.x.
[38] Guo J, Nguyen A, Banyard DA, Fadavi D, Toranto JD, Wirth GA, et al. Stromal vascular fraction: a regenerative reality? Part 2: mechanisms of regenerative action. J Plast Reconstr Aesthet Surg 2016;69:180–8, http://dx.doi.org/10.1016/j.bjps.2015.10.014.
[39] Conrad C, Huss R. Adult stem cell lines in regenerative medicine and reconstructive surgery. J Surg Res 2005;124:201–8, http://dx.doi.org/10.1016/j.jss.2004.09.015.
[40] van Rijssen AL, Werker PMN. Percutaneous needle fasciotomy in Dupuytren's disease. J Hand Surg Edinb Scotl 2006;31:498–501, http://dx.doi.org/10.1016/j.jhsb.2006.03.174.
[41] Pess GM, Pess RM, Pess RA. Results of needle aponeurotomy for Dupuytren contracture in over 1.000 fingers. J Hand Surg 2012;37:651–6, http://dx.doi.org/10.1016/j.jhsa.2012.01.029.
[42] Hurst LC, Badalamente MA, Hentz VR, Hotchkiss RN, Kaplan FTD, Meals RA, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med 2009;361:968–79, http://dx.doi.org/10.1056/NEJMoa0810866.
[43] Watt AJ, Curtin CM, Hentz VR. Collagenase injection as nonsurgical treatment of Dupuytren's disease: 8-year follow-up. J Hand Surg 2010;35:534–9, http://dx.doi.org/10.1016/j.jhsa.2010.01.003.
[44] Castiglione F, Hedlund P, Van der Aa F, Bivalacqua TJ, Rigatti P, Van Poppel H, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. Eur Urol 2013;63:551–60, http://dx.doi.org/10.1016/j.eururo.2012.09.034.
[45] Alfarano C, Roubeix C, Chaaya R, Ceccaldi C, Calise D, Mias C, et al. Intraparenchymal injection of bone marrow mesenchymal stem cells reduces kidney fibrosis after ischemia-reperfusion in cyclosporine-immunosuppressed rats. Cell Transplant 2012;21:2009–19, http://dx.doi.org/10.3727/096368912X640448.
[46] Elnakish MT, Kuppusamy P, Khan M. Stem cell transplantation as a therapy for cardiac fibrosis. J Pathol 2013;229:347–54, http://dx.doi.org/10.1002/path.4111.
[47] Dazzi F, Horwood NJ. Potential of mesenchymal stem cell therapy. Curr Opin Oncol 2007;19:650–5, http://dx.doi.org/10.1097/CCO.0b013e3282f0e116.
[48] Dolmans GH, Werker PM, Hennies HC, Furniss D, Festen EA, Franke L, et al. Wnt signaling and Dupuytren's disease. N Engl J Med 2011;365:307–17, http://dx.doi.org/10.1056/NEJMoa1101029.
[49] Verhoekx JSN, Mudera V, Walbeehm ET, Hovius SER. Adipose-derived stem cells inhibit the contractile myofibroblast in dupuytren's disease. Plast Reconstr Surg 2013;132:1139–48, http://dx.doi.org/10.1097/PRS.0b013e3182a3bf2b.
[50] Hovius SER, Kan HJ, Smit X, Selles RW, Cardoso E, Khouri RK. Extensive percutaneous aponeurotomy and lipografting: a new treatment for Dupuytren disease. Plast Reconstr Surg 2011;128:221–8, http://dx.doi.org/10.1097/PRS.0b013e31821741a.
[51] Morell-Dubois S, Condette-Wojtasik G, Clerson P, Berezné A, Launay D, Lambert M, et al. Complaints, needs of patients with systemic sclerosis: a better understanding for a better care. Rev Med Interne 2011;32:537–43, http://dx.doi.org/10.1016/j.revmed.2011.02.004.
[52] Rannou F, Poiraudeau S, Berezné A, Baubet T, Le-Guern V, Cabane J, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ) Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007;57:94–102, http://dx.doi.org/10.1002/art.22468.
[53] Serratrice N, Bruzzese L, Magalon J, Véran J, Giraudo L, Aboudou H, et al. New fat-derived products for treating skin-induced lesions of scleroderma in nude mice. Stem Cell Res Ther 2014;5:138, http://dx.doi.org/10.1186/scrt528.
[54] Bank J, Fuller SM, Henry GI, Zachary LS. Fat grafting to the hand in patients with Raynaud phenomenon: a novel therapeutic modality. Plast Reconstr Surg 2014;133:1109–18, http://dx.doi.org/10.1097/PRS. 0000000000000104.
[55] Del Papa N, Di Luca G, Sambataro D, Zaccara E, Maglione W, Gabrielli A, et al. Regional implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting indolent digital ulcers in patients with systemic sclerosis. Cell Transplant 2015;24:2297–305, http://dx.doi.org/10.3727/096368914X685636.
[56] Granel B, Daumas A, Jouve E, Harlé J-R, Nguyen P-S, Chabannon C, et al. Safety, tolerability and potential efficacy of injection of autologous adipose-derived stromal vascular fraction in the fingers of patients with systemic sclerosis: an open-label phase I trial. Ann Rheum Dis 2015;74:2175–82, http://dx.doi.org/10.1136/annrheumdis-2014-205681.
[57] Guillaume-Jugnot P, Daumas A, Magalon J, Jouve E, Nguyen P-S, Truillet R, et al. Autologous adipose-derived stromal vascular fraction in patients with systemic sclerosis: 12-month follow-up. Rheumatology 2016;55:301–6, http://dx.doi.org/10.1093/rheumatology/kev323.
[58] Lendeckel S, Jödicke A, Christophis P, Heidinger K, Wolff J, Fraser JK, et al. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report. J Craniomaxillofac Surg 2004;32:370–3, http://dx.doi.org/10.1016/j.jcms.2004.06.002.
[59] Thesleff T, Lehtimäki K, Niskakangas T, Mannerström B, Miettinen S, Suuronen R, et al. Cranioplasty with adipose-derived stem cells and biomaterial: a novel method for cranial reconstruction. Neurosurg 2011;68:1535–40, http://dx.doi.org/10.1227/NEU.0b013e31820ee24e.
[60] Wilson SM, Goldwasser MS, Clark SG, Monaco E, Bionaz M, Hurley WL, et al. Adipose-derived mesenchymal stem cells enhance healing of mandibular defects in the ramus of swine. J Oral Maxillofac Surg 2012;70:e193–203, http://dx.doi.org/10.1016/j.joms.2011.10.029.

[61] Lin Y, Luo E, Chen X, Liu L, Qiao J, Yan Z, et al. Molecular and cellular characterization during chondrogenic differentiation of adipose tissue-derived stromal cells in vitro and cartilage formation in vivo. J Cell Mol Med 2005;9:929–39.
[62] Zhang H-N, Li L, Leng P, Wang Y-Z, Lv C-Y. Uninduced adipose-derived stem cells repair the defect of full-thickness hyaline cartilage. Chin J Traumatol 2009;12:92–7.
[63] Bahrani H, Razmkhah M, Ashraf MJ, Tanideh N, Chenari N, Khademi B, et al. Differentiation of adipose-derived stem cells into ear auricle cartilage in rabbits. J Laryngol Otol 2012;126:770–4, http://dx.doi.org/10.1017/S0022215112001065.
[64] di Summa PG, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. J Plast Reconstr Aesthetic Surg 2010;63:1544–52, http://dx.doi.org/10.1016/j.bjps.2009.09.012.
[65] Mohammadi R, Sanaei N, Ahsan S, Rostami H, Abbasipour-Dalivand S, Amini K. Repair of nerve defect with chitosan graft supplemented by uncultured characterized stromal vascular fraction in streptozotocin induced diabetic rats. Int J Surg Lond Engl 2014;12:33–40, http://dx.doi.org/10.1016/j.ijsu.2013.10.018.
[66] Papalia I, Raimondo S, Ronchi G, Magaudda L, Giacobini-Robecchi MG, Geuna S. Repairing nerve gaps by vein conduits filled with lipoaspirate-derived entire adipose tissue hinders nerve regeneration. Ann Anat 2013;195:225–30, http://dx.doi.org/10.1016/j.aanat.2012.10.012.
[67] Butterwick KJ. Rejuvenation of the aging hand. Dermatol Clin 2005;23:515–27, http://dx.doi.org/10.1016/j.det.2005.04.007 [vii].
[68] Tsumuraya T, Ohtaki H, Song D, Sato A, Watanabe J, Hiraizumi Y, et al. Human mesenchymal stem/stromal cells suppress spinal inflammation in mice with contribution of pituitary adenylate cyclase-activating polypeptide (PACAP). J Neuroinflammation 2015;12:35, http://dx.doi.org/10.1186/s12974-015-0252-5.
[69] Araña M, Gavira JJ, Peña E, González A, Abizanda G, Cilla M, et al. Epicardial delivery of collagen patches with adipose-derived stem cells in rat and minipig models of chronic myocardial infarction. Biomaterials 2014;35:143–51, http://dx.doi.org/10.1016/j.biomaterials.2013.09.083.
[70] van Dijk A, Naaijkens BA, Jurgens WJ, Nalliah K, Sairras S, van der Pijl RJ, et al. Reduction of infarct size by intravenous injection of uncultured adipose derived stromal cells in a rat model is dependent on the time point of application. Stem Cell Res 2011;7:219–29, http://dx.doi.org/10.1016/j.scr.2011.06.003.
[71] Rodriguez J, Boucher F, Lequeux C, Josset-Lamaugarny A, Rouyer O, Ardisson O, et al. Intradermal injection of human adipose-derived stem cells accelerates skin wound healing in nude mice. Stem Cell Res Ther 2015:6, http://dx.doi.org/10.1186/s13287-015-0238-3.
[72] Li Y, Zhang W, Gao J, Liu J, Wang H, Li J, et al. Adipose tissue-derived stem cells suppress hypertrophic scar fibrosis via the p38/MAPK signaling pathway. Stem Cell Res Ther 2016:7, http://dx.doi.org/10.1186/s13287-016-0356-6.
[73] Gentile P, De Angelis B, Pasin M, Cervelli G, Curcio CB, Floris M, et al. Adipose-derived stromal vascular fraction cells and platelet-rich plasma: basic and clinical evaluation for cell-based therapies in patients with scars on the face. J Craniofac Surg 2014;25:267–72, http://dx.doi.org/10.1097/01.scs.0000436746.21031.ba.
[74] Baptista C, Iniesta A, Nguyen P, Legré R, Gay A-M. Greffe de tissu adipeux autologue dans la prise en charge chirurgicale des cicatrices douloureuses: résultats préliminaires. Chir Main 2013;32:329–34, http://dx.doi.org/10.1016/j.main.2013.07.006.
[75] Oshita T, Tobita M, Tajima S, Mizuno H. Adipose-derived stem cells improve collagenase-induced tendinopathy in a rat model. Am J Sports Med 2016;44:1983–9, http://dx.doi.org/10.1177/0363546516640750.
[76] Chen H-S, Su Y-T, Chan T-M, Su Y-J, Syu W-S, Harn H-J, et al. Human adipose-derived stem cells accelerate the restoration of tensile strength of tendon and alleviate the progression of rotator cuff injury in a rat model. Cell Transplant 2015;24:509–20, http://dx.doi.org/10.3727/096368915X686968.
[77] Moumas A, Gay A, Legré R. Greffe de tissu adipeux autologue dans la prise en charge des épicondylites : résultats d'une étude préliminaire. Chir Main 2010;29:373–7, http://dx.doi.org/10.1016/j.main.2010.09.011.
[78] Coleman SR. Hand rejuvenation with structural fat grafting. Plast Reconstr Surg 2002;110:1731–44, http://dx.doi.org/10.1097/01.PRS.0000033936.43357.08 [discussion 1745-7].
[79] Agostini T, Perello R, Lipomodeling:. An innovative approach to global volumetric rejuvenation of the hand. Aesthetic Surg J Am Soc Aesthetic Plast Surg 2015;35:708–14, http://dx.doi.org/10.1093/asj/sju163.