The use of stem cells in aesthetic dermatology and plastic surgery procedures. A compact review of experimental and clinical applications

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Abstract

The aim of this paper was to collect currently available data related to the use of stem cells in aesthetic dermatology and plastic surgery based on a systemic review of experimental and clinical applications. We found that the use of stem cells is very promising but the current state of art is still not effective. This situation is connected with not fully known mechanisms of cell interactions, possible risks and side effects. We think that there is a big need to create and conduct different studies which could resolve problems of stem cells use for implementation into aesthetic dermatology and plastic surgery.

Key words: stem cells, aesthetic dermatology, plastic surgery.

Introduction

After many conducted experimental projects in the last decades of the 20th century, stem cells (SC) were around twenty years ago announced as an innovative and promising remedy for many different diseases [1–4]. This hope related with specific properties of stem cells and their expected regenerative potential increases in direct proportion to the significant need in many medical specialties. Different scientific groups have started their projects on various preclinical and clinical levels focused only on the novel SC application methods and their use in alternative therapeutic protocols [5–8]. Thanks to many achievements resulting from basic, preclinical and translational experiments in 1992, the American scientist and writer Leland Kaiser established a new term “regenerative medicine” [9, 10]. This term determines a new branch of medicine focused on effective SC implementation in patients with different chronic diseases [11–13]. The most known examples of SC introduction into treatment procedures are mostly connected with transplantation of hematopoietic stem cells (HSCT) and skin and adipose tissue grafting [14, 15]. The data published by Eurostemcell show that SC are currently used in clinic in a very limited number of procedures and beside hematology or reconstructive surgery they are used mainly in skin grafts, which are prepared for severe burn trauma patients, or in ophthalmology in limbus corneal stem cell transplantation [16–18]. Beside the fact that hematopoietic stem cells were first transplanted to a patient with an irradiation injury 60 years ago and in Europe they are currently transplanted in more than 26 000 patients yearly, there is still a serious problem with fulfillment
of the basic assumptions of regenerative medicine associated mainly with the solid organ regeneration and a simple SCs administration for each patient suffering from any chronic disease [4, 19, 20]. That is why, especially many last year’s planned and conducted projects were considered with a potential supportive role and use of stem cells in such specialties like aesthetic dermatology and plastic surgery [21].

The aim of this work was to analyze and present in a compact review current achievements and knowledge about the use of stem cells in experimental and clinical aesthetic dermatology procedures.

Potential stem cells sources and their implementation in current experimental and clinical aesthetic dermatology and plastic surgery

Stem cells are currently intensively investigated for applications in a number of medical disorders including dermatological ones [22]. Mesenchymal stem cells (MSCs) seem to be an ideal source for tissue engineering applications due to the lack of ethical concerns, high availability and increasing number of methods for isolation and expansion of such cell types. Each year on the market we can see new devices for MSCs expansion and culture, which allows to obtain a large number of cells, suitable for clinical application. Ability to differentiate into many cell types and lack of confirmed tumorigenic properties in comparison to embryonic stem cells or induced pluripotent stem cells, additionally argues for mesenchymal stem cells [23].

In dermatology and aesthetic surgery, a lot of disorders, currently incurable or with insufficient results after treatment, like psoriasis vulgaris, epidermolysis bullosa, systemic sclerosis, scleroderma, extensive burns, can be potentially the target of stem cell therapy (Table 1). Among MSCs, in dermatology the most popular ones include adipose derived stem cells (ADSCs) used alone after expansion in vitro or together with stromal vascular fraction (SVF) [24]. The first method is cost and time consuming but instead we obtain homogenous cells fraction with a fully defined phenotype. The use of SVF is cheaper and it could be applied during one surgical procedure. After their isolation and centrifugation, lipoaspirates could be directly applied to a patient. The disadvantage is a heterogeneous cell fraction; that is why it is not clear which cell type is responsible for regeneration processes [25]. It is possible to find on the market systems for automatic isolation of ADSCs, such terminology is misleading because cells isolated in such way will still be composed of heterogeneous or mixed population of cells found in adipose tissue [26]. The only way to obtain the appropriate number and homogenous adipose-derived stem cell population is its in vitro culture after isolation. Stromal vascular fraction is composed of fibroblasts, endothelial cells, smooth muscle cells, pericytes, immune cells and preadipocytes. The culture of SVF over time leads to elimination of most of these cell types leaving the population primarily composed of preadipocytes that display characteristics of multipotent stem cells [27].

Adipose derived stem cells were analyzed as a cell source for the full-thickness skin defect repair. Compared to control, cell therapy resulted in scar size reduction and provide better color quality and pliability of skin [28]. Stromal vascular fraction containing ADSCs was also used for treatment of face scars. This fraction was applied together with fat grafting which enhanced contour restoring compared to control in 1 year’s follow-up [29]. Autologous fat grafting, containing ADSCs, was used for scar treatment on 20 patients in another study [30]. Application of this method leads to satisfactory aesthetic and functional results. This technique eliminated the pain and increased scar elasticity. Stem cells from lipoaspirates loaded into poly-3-hydroxybutyrate-co-hydroxyvalerat (PHBV) scaffold were examined on a mice model for full-thickness wound healing [31]. Twenty-eight days after implantation wounds were closed and PHBV scaffold degraded completely. The PHBV scaffold together with ADSCs creates an optimal combination for wound healing. Scaffold induced scarring reduction while stem cells enhanced vascularization. Promising results were also observed when adipose-derived stem cells were applied with small intestine submucosa (SIS) scaffold [32]. In another study, ADSCs isolated from lipoaspirates was used alone, without scaffold, for treatment of skin defects on the facial area in 4 patients [33]. Stem cells in high density were applied on extracellular matrix consisting of squeezed fat directly to the defect location. Defects were repaired in all patients and used ADSCs showed excellent wound healing properties. Therapy using stem cells expanded in vitro is still relatively expensive, that is why authors of the mentioned publication concluded that such therapy is restricted to small defects. Our observations are similar, larger defects need using more stem cells. To obtain the proper cell number for cellular therapy, stem cells after isolation have to be expanded in vitro. In our unpublished data, we proved that ADSCs seeded at a density of 10 million cell per cm² of scaffold gives a significant improvement in bladder regeneration with a reduction of scar formation compared to lower cell density and acellular scaffold. We have to remember that scaffold used for urinary tract regeneration is flat material (below 1 mm thickness), and defects in plastic surgery are much deeper. Expansion of the cell number in vitro needs using a large number of plastic culture flasks and culture media together with proper supplements which are still quite expensive. A similar experiment was conducted on 2 patients with necrosis and acute inflammatory reaction after facial filler injections [34]. In both cases satisfactory results were achieved. Another approach is differentiation of ADSCs obtained from...
lipoaspirates into adipocytes [35]. After in vitro differentiation, cells were injected subcutaneously to the scar in 31 patients. Twelve-week follow up resulted in scar size reduction. The proposed therapy was safe without any significant side effects. Hypertrophic scar reduction was also observed after application of ADSCs on a rabbit ear model [36]. In another study, a comparison of ADSCs with dermal fibroblasts was performed on a mice model. Cells were applied on a wound in collagen gel [37]. Both cells stimulated wound healing, however a greater effect was observed in the case of fibroblasts. The conditioned medium obtained from ADSCs culture combined with fractional carbon dioxide laser resurfacing improved treatment of atrophic acne scars and skin rejuvenation. Combined therapy resulted in increased elasticity and hydration of the skin, increased collagen and elastin density and its proper arrangement. Overall satisfaction of the subjects was also noticed [38]. Wrinkles reduction using stem cell therapy was also considered. The skin of BALB/c nude rats was exposed to UV-B radiation to induce photoaged wrinkles after which ADSCs and fibroblast cells (control group) were applied. In both groups, wrinkles reduction was noted, a better effect was observed in the ADSCs group however both cell types induced collagen and metalloproteinase (MMP) production [39]. This cell type influence anti-aging properties by inhibition of melanin production after UV exposure resulting in skin whitening [40]. An anti-aging effect of stem cells from adipose tissue may result from glycation suppression, antioxidation and trophic effect, which in consequence leads to restoration of the functional capacity of the skin [41].

Bone marrow (BM) is another cell source frequently used for tissue engineering application in dermatology. The MSCs isolated from BM, similarly like ADSCs are well characterized and have excellent regenerative potential. The main factor that differs these two cell types is the

| No. | Cell type     | Condition                          | Number of patients | Number     |
|-----|---------------|------------------------------------|--------------------|------------|
| 1   | UC-MSCs       | Psoriasis vulgaris                 | 30                 | NCT02491658 |
| 2   | ADSCs         | Lipodystrophies                    | 25                 | NCT02034786 |
| 3   | ADSCs         | Romberg's disease                  | 30                 | NCT02494752 |
|     |               | Craniofacial microsoma            |                    |            |
|     |               | Lipodystrophy                      |                    |            |
|     |               | Mixed connective tissue disease    |                    |            |
| 4   | ADSC-SVF      | Safety of ADSC-SVF in:             | 10                 | NCT02590042 |
|     |               | Abnormally healing wounds          |                    |            |
|     |               | Scars                              |                    |            |
|     |               | Soft tissue defects                |                    |            |
| 5   | ADSC-SVF      | Safety of ADSC-SVF in:             | 6                  | NCT01828723 |
|     |               | Lipoatrophy                        |                    |            |
|     |               | Aging                              |                    |            |
|     |               | Wrinkles                           |                    |            |
| 6   | BM-MSCs       | Intrinsic aging of skin            | 29                 | NCT01771679 |
|     |               | Chronic effect of ultraviolet radiation on normal skin (photo-aging) | | |
|     |               | Dermatologic disorders             |                    |            |
| 7   | ADSCs         | Micromastia                        | 20                 | NCT02116933 |
| 8   | ADSC-SVF      | Breast neoplasms                   | 10                 | NCT01801878 |
|     |               | Skin abnormalities                 |                    |            |
| 9   | UC-MSCs       | Wounds                             | 30                 | NCT02672280 |
|     |               | Diabetic foot ulcers               |                    |            |
|     |               | Burns                              |                    |            |
| 10  | PBSCT         | Systemic scleroderma               | 19                 | NCT00278525 |
| 11  | UC-MSCs       | Burns                              | 20                 | NCT01443689 |
| 12  | BM-MSCs       | Scleroderma                        | 15                 | NCT00040651 |
|     |               | Systemic sclerosis                 |                    |            |

PBSC – peripheral blood stem cell transplantation, UC-MSCs – umbilical cord mesenchymal stem cells, ADSCs – adipose-derived stem cells, SVF – stromal vascular fraction, BM-MSCs – bone marrow mesenchymal stem cells.
source of cells. Isolation from bone marrow is a more invasive and harmful procedure for patients [42].

BM-MSCs isolated from BM aspiration after granulocyte colony-stimulating factor (G-CFS) stimulation were used for acute scars treatment. The study was performed on 14 patients, 6 months after treatment with a single dose of BM-MSCs, a significant improvement without any side-effects was observed [43]. Study utilizing the conditioned medium (CM) from bone-marrow MSCs was used for wrinkles treatment. An experiment performed on a rat model showed that CM from BM-MSCs increase pro-collagen synthesis in a dose-dependent manner inducing skin damage repair after UV action [44]. After intra-venous administration, BM-MSCs migrate to the wound site and stimulate the wound repair, which was confirmed on a mice model [45]. A combination of these cells with collagen sponges was applied for wound healing in mice. Obtained results showed that such connection is a promising way for soft tissue regeneration [46].

Autologous BM-MSCs in fibrin spray after approximately 2-week in vitro expansion was used for treatment of acute and chronic non-healing wounds in 10 patients [47]. In acute wounds, complete healing was observed 7–8 weeks after the procedure and within 16–20 weeks in patients with chronic wounds. BM-MSCs were also used for preventing contractions of skin grafts after transplantation in a patient with hypertrophic scars [48]. Stem cells were transplanted into the scar excision wound and then covered with decellularized dermal matrix and next with split-skin graft. After 2-year follow up, the proposed approach resulted in contraction reduction. Some studies suggest that all bone marrow cells have better regenerative potential in wound healing in comparison to more manipulated in vitro pure BM-MSCs [49].

Other cell sources like amniotic fluid stem cells (AFSCs), umbilical cord blood stem cells (UB-MSCs) or Warthon’s jelly (WI-MSCs) were also considered for application in dermatological disorders [50, 51]. These cell types have greater proliferative and differentiation potential compared to ADSCs and BM-MSCs. A disadvantage is availability of cells for regenerative purposes. Umbilical cord blood allows to obtain a small number of cells, which is not sufficient for majority of clinical disorders, even after in vitro expansion [52]. The amniotic fluid is collected during planned amniocentesis, during which a small number of material can be obtained, and similarly like in case of UB-MSCs, generation of an appropriate cell number is difficult. Additionally, the amniotic fluid (AF) collection is associated with a risk of fetus damage [53].

Two million AFSCs together with amniotic membrane matrix were injected directly into the thoracotomy scar [54]. Substantial tissue remodeling and full relief of pain was observed about 12 weeks after therapy initiation, cells were delivered three times. Mesenchymal stem cells derived from the umbilical cord and WI-MSCs were examined on a mice wound full-thickness defect model. Advantages of wound healing and wound re-epithelialization after cell implantation were not observed in both cases compared to controls [55]. The paracrine effect of WI-MSCs may be responsible for skin wound healing promotion. Experiments performed in vitro and in vivo on a mouse model indicated that this cell source enhanced expression of genes responsible for wound healing and positively regulates cell survival, proliferation and migration [56]. A combination of WI-MSCs seeded on the decellularized amniotic membrane creates a great connection for skin injury treatment having better healing results with hair growth compared to the injection of MSCs alone [57].

The current technical aspects of stem cells obtaining and their application methods

Gimble et al. characterized in a precise way the most important factors related to the procedures created for most effective receiving of stem cells. Those authors suggest that SCs should be always obtained in a safe way using a minimally invasive procedure from the anatomical regions constituting biologically wealthy niches for a potentially large number of stem cells, which could be later simply used directly or could be prepared using Good Manufacturing Practice (GMP) guidelines for several different medical procedures [58]. The most promising types of stem cells which could meet these criteria include ADSC [21, 59]. This group of cells is a great hope for current aesthetic dermatology and plastic surgery mainly because of the well-known and described, and what is most important, very widely used fat grafting methods based on centrifuged and noncentrifuged fat [60, 61]. The simple potentially translational process of fat transfer methodology and SCs separation with later cell cultivation has been presented in Figure 1. One of very interesting and still controversial technical aspects connected with novel SCs application methods in different medical specialties is the selection of place from which the SC should be derived [62, 63]. As mentioned before, many authors suggest that especially for the aesthetic procedures, the best “first choice” select option is the use of transferred fat [64, 65]. The most effective potential SC sources based on anatomical regions for fat transfer are presented in Figure 2.

Possible positive effects, emerging clinical problems and side effects

Aesthetic dermatology and plastic surgery are strongly connected with two medical and social terms: 1) patient satisfaction and 2) possible side effects [66, 67]. It could be also stated that both terms directly result from the specificity of both specializations where the patient finds himself mainly as a consumer and expects only fully satisfactory changes in appearance [68, 69]. It should be also indicated that the topics associated with the pos-
Possible side effects of any procedures used in aesthetic dermatology and plastic surgery should be always considered as first when planning the treatment strategy, and always during the various stages of the natural learning curve by dermatological and surgical beginners [70–72]. This rule applies also to the use of methods which are introduced as novel. Such innovative concepts include the topics of stem cell implementation. The full and precise evaluation and standard assessment of potential positive effects, emerging clinical problems and possible side effects in this scientific area is still problematic as it was shown in previous chapters due to the fact that there is still significant preponderance of basic and pre-clinical studies on expanded clinical trials [73]. This situation affects also the fact that currently only some projects have achieved the second phase of clinical trials or have obtained the acceptance and approval of the Federal Drug Administration (FDA), European Medicines Agency (EMA) and other representative supervision and legal agencies or institutes [74]. The most known representative examples include the project registered by Antria number # NCT02526576 concerning to the use of SVC containing adipose derived stem cells in facial fat grafting. The general and compact assessment based on representative statistical analysis of the possible positive effects, emerging clinical problems and side effects is problematic due to the lack of thematic publications. As at the date of this publication, for example in spontaneous analysis of Pubmed records, the result for prefix ADSC with other selectively chosen thematic words showed: (ADSC + "selected word") = 47 including words: aesthetic (23), dermatology (11), skin (47), rejuvenation (3), anti-aging (4), and cosmetic (8). As compared to the ADSC with words "plastic surgery" added, the number of records was 75.

Figure 2. The most effective potential of SC sources based on currently top selected anatomical regions for fat transfer.
The use of stem cells in aesthetic dermatology and plastic surgery procedures. A compact review of experimental and clinical applications

Conclusions

Almost 80% of currently published reviews from the field of regenerative medicine in which the topic of the stem cell use in clinic is discussed are titled with a perverse question: how far we are currently with our knowledge about the potential use of SCs in different medical specialties and what we know about their effectiveness, indications for such procedures and their possible side effects [89]. That is why many authors title their work with short phrases like: stem cells hype or hope, stem cell myths and much more other statements [90]. This situation is related also to the papers concerning the implementation of SCs during aesthetic procedures where some authors refer to significance of this novel therapeutic option and directly demonstrate if SCs are now the fact or still fiction and futuristic concept [91]. There are also many papers in which the authors critically or very deeply but without hard and clear final statements, discuss the future of stem cell application and their use in clinic [92].

The natural search for new treatment possibilities together with a highly developing and large business market is very fast influenced by implementation of the topic “stem cells” in the classic and aesthetic dermatology and plastic surgery. For proper understanding of such intensive search for new and effective procedures, the following the fact is important – the invasive and non-invasive cosmetic procedures market is estimated at 12.5 billion dollars in the US yearly with a great representative number of non-surgical procedures of 10,591,506 in 2014 [93]. The data published by the International Society of Aesthetic Plastic Surgery (ISAPS) in the International Survey on Aesthetic/Cosmetic Procedures performed in 2014 present the number of non-surgical procedures counted and registered for European countries like Germany or France at around 1 million procedures in both. The demand for such procedures is still growing, and the estimated increase in the number of such procedures oscillates at around 750% comparing each decade [94].

### Table 2. Selected potential positive effects of the use of stem cells in aesthetic dermatology and plastic surgery procedures

| Type of suggested procedure using stem cells | Type of suggested cells | Potential positive effects/positive influence/indications | References |
|---------------------------------------------|-------------------------|----------------------------------------------------------|------------|
| Direct cell injection onto affected region  | Adipose-derived stem cells (ADSCs) | Individual treatment to support the wound healing process in complications after the previous filler injection | Kim et al. [77] |
| Cell-assisted lipotransfer (CAL)            | Adipose-derived SVF (stromal vascular fraction) cells | Good aesthetic results in treatment of breast augmentation and facial lipoatrophy | Mehrabani et al. [25] |
| Direct targeted supporting implementation during platelet-rich plasma injection | Adipose-derived stem cells (ADSCs) | Optimal scar reduction | Eun [78] |
| Stem cell-enriched tissue injections (SET)  | Traditionally prepared fat grafts with adipose-derived regenerative cells (ADRCs) | Effective influence on fat-grafting procedures performed especially in fibrosis and post radiation cases | Tiryaki et al. [79] |
| Implementation of integrated mesenchymal stem cells with fibrin glue into the dressing of burn wounds | Bone marrow-derived stem cells (BM-MSCs) | Significantly faster healing of plastic development of burn wounds | Gnieh et al. [80] |
| Stem cell intravenous injection             | Human umbilical cord-derived mesenchymal stem cells (UC-MSCs) | Significantly increased neovascularization and better burn wound healing | Gnieh et al. [80] |
| Direct subcutaneous injection              | Adipose-derived stem cells (ADSCs) | Skin anti aging and regenerative effect | Zhang et al. [83] |

### Table 3. Main possible risk factors and side effects suggested in the literature related to the use of SC in medical procedures

| Possible side effects and risks | References |
|--------------------------------|------------|
| Rejection of stem cells        | Herberts et al. [84] |
| Neoplasm formation             | Arnhold et al. [85] |
| Undesired immune response      | Herberts et al. [84] |
| Uncontrolled (non-planned) differentiation | Fortin et al. [86] |
| Unexpected cell contamination  | Torsvik et al. [87] |
| Unsatisfactory clinical effect  | Thomsen et al. [88] |
Such big need and still growing patient expectations like better final outcome or longer persistence of the aesthetic effect obtained, to some degree has influenced also the faster creation of new projects based on the translational and experimental studies oriented at the use of SCs. In this paper we have presented the potential stem cells sources and their implementation in current experimental and clinical aesthetic dermatology and plastic surgery applications. We have supported this material also with data related to the current technical aspects of stem cells obtaining and their application methods. We have discussed the possible positive effects, emerging clinical problems and side effects.

In comprehensively analyzed material we have found that there is still a lack of fully translational and advanced clinical studies in which the use of SCs could be successfully assessed. There are still no randomized or large cohort group data from the field of aesthetic dermatology and plastic surgery from which the hard or large cohort group data from the field of aesthetic dermatology and plastic surgery from which the hard arguments pro or against SC use in different aesthetic procedures could be formulated. But in the literature one can find a lot of basic and pre-clinical in vitro and in vivo studies with promising results. Those projects are mainly related to the SC obtained due to the fat liposuction procedure with flagship application ideas of ADSC.

In our opinion, the use of stem cells in aesthetic dermatology and plastic surgery procedures is very promising but currently still not possible and according to the current state of art, not effective. This situation is related to still not fully known mechanisms of cell interactions and possible risks and side effects. We think that there is still a big need to create and conduct different basic and pre-clinical studies which could resolve current problems of SC use and can significantly accelerate their implementation into aesthetic dermatology and plastic surgery.

**Conflict of interest**

The authors declare no conflict of interest.

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The use of stem cells in aesthetic dermatology and plastic surgery procedures. A compact review of experimental and clinical applications

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Advances in Dermatology and Allergology 6, December / 2017

534

Advances in Dermatology and Allergology 6, December / 2017

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