



POSSIBILITIES OF USING TRANSPLANTATION OF AUTOLOGICAL ADIPITY TISSUE ENRICHED IN STEM CELLS IN MAMMOPlasty.

Abduaxatov Abdulaziz Abduazizovich

Razokov Baxodir Utkirovich

Maxmudov Begzod Kurbonbekovich

Samarkand State Medical University

Uzbekistan. Samarkand

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Introduction

Every year, the number of cases of mammoplasty performed for cosmetic reasons increases. However, operations on the mammary glands (MG) are often performed not only for aesthetic reasons. The trend of increasing incidence of breast cancer (BC) in women continues [1–3]. Among the technologies for combined treatment of patients with breast cancer, the surgical method remains fundamental. Moreover, both radical mastectomy and partial resections of gl.mammae after surgery are invariably accompanied by the formation of breast deformities. The latter causes a deterioration in the quality of life of women with breast cancer, reducing the possibility of their rapid social adaptation [4].

Autologous adipose tissue (ATT) is a unique plastic material used to eliminate soft tissue defects of various anatomical locations. The experience of using AVT for these purposes is given in the classic works of G. Neuber [5] and E. Lexer [6]. However, only the development of technologies for isolating mesenchymal stem cells (MSCs) from human AAT allowed us to consider the possibilities of adipose tissue transplantation (AT) in a new light, using the principles of regenerative medicine [7–10]. Stem cells from AVT are similar in cytological properties to bone marrow SCs, and the possibilities for their use are wider due to the relative ease of isolation [9, 11].

Scientific literature provides information on cases of transplantation of AVT enriched with SA to correct the shape and volume of the mammary glands, both for aesthetic reasons and in cases of elimination of postoperative deformities. However, the results presented by the authors of these publications are ambiguous. The need for a comprehensive assessment of the experience of using SCs from VT in plastic and reconstructive surgery of the breast appears to be an incentive for a special study of materials on this topic.

Material and research methods

To collect scientific medical information, the <https://www.ncbi.nlm.nih.gov/pubmed>, <http://www.cochranlibrary.com/>. The





information contained in 985 literature sources published between 2008 and 2017 was studied, among which the content of 47 publications was analyzed purely on the topic of research.

Research results and discussion

About methods of obtaining MSCs from AST. Cytological features and possibilities of using SC as an autologous material for eliminating soft tissue deformations. Many authors consider cell-associated lipotransfer (CBL), proposed by D. Matsumoto et al., to be the main method for improving the results of autoadipotransplantation. in 2006 [12]. Researchers think so because this technology involves enriching the transplanted adipose tissue with MSCs. In this regard, the search for optimal ways to obtain fat for isolating MSC culture seems to be one of the significant directions in studying the possibilities of using this type of cellular material in clinical practice [13–15]. Some researchers report positive results of collecting VT using vacuum aspiration from donor sites of the human body [16]. Other authors believe that it is better to obtain VT for isolating MSC culture through lipectomy [17]. A number of experts are convinced that the method of collecting VT does not significantly affect the amount of SC isolated from it [18].

In the works of N. Gnanasegaran et al. [15] showed that the levels of gene expression and the potency of SCs from AT to a certain differentiation are determined by the method of obtaining tissue material during liposuction/lipectomy.

After harvesting the ATF, the SC culture is isolated from it. The most common method for isolating SC from AT is the enzymatic cleavage of lipoaspirate (LA) into cells of the stromal vascular fraction (SVF), containing stem, stromal and endothelial cell elements, pericytes, leukocytes, erythrocytes and a number of non-cellular by-products [19]. Dispase, trypsin, but most often collagenase are used to ferment fat. First, the LA is washed with a sterile solution of phosphate buffer until the substrate turns golden, then treated with a solution of collagenase in phosphate buffer. The resulting mixture is kept in a thermostat at a temperature of 37 °C, after which its lower layer is transferred into test tubes and centrifuged. The sediment consists of SSF cells, which are resuspended in control media, counted and placed in separate flasks with a concentration of 1×10^6 cells. In general, more than 1×10^7 SSF cells are obtained from 20 mg of lipoaspirate [14].

The possibility of isolating SCAT from LA using non-enzymatic methods is based on the fact that after LS, stem cells are located at the bottom of the





aspiration container. Cells isolated by a non-enzymatic method are phenotypically and in terms of differentiation ability no different from those obtained by LA fermentation, but their number ultimately turns out to be 19–20 times less [14, 20, 21].

In 2006, the International Society of Cell Therapy (ISCT) defined a set of cytological criteria for identifying VT MCs [22]. It includes plastic adhesiveness under standard culture conditions; expression of CD73, CD90 and CD105; lack of expression of CD45, CD34, CD14 or CD11b, CD19 or CD79 α and HLA-DR surface molecules [22]. In 2013, MOCT identified additional positive markers (CD13, CD29 and CD44) detected on the surface

VT SC in more than 80% of cases, and CD31, CD45 and CD235a are regarded as the main negative markers, since they are found on the surface of VT in less than 2% of cases [19]. To phenotype cells as mesenchymal multipotent on the surface of SCs, the presence of at least two positive and two negative markers is necessary, and the viability of cellular elements must exceed 70%. In addition, isolated SCs must have the ability to differentiate into osteoblasts, adipocytes and chondroblasts [23].

In general, the main features of VT SCs are the relative ease of their production with minimal surgical trauma to the donor area of the patient's body and the possibility of differentiation, similar to other types of MSCs [7, 11]. According to some researchers, it is important that AT SCs are characterized by more pronounced proliferation and cultivation capabilities compared to bone marrow SCs [24–26]. The ability of VT SCs to differentiate not only into adipocytes, but also into osteoblasts, chondrocytes, myocytes, epithelial cells and neurons makes their potential use for the restoration of many tissues of the human body possible [7].

Identification of the unique ability of SCs from adipose tissue to regenerate, secrete trophic factors, and differentiate into various cell types turned out to be a prerequisite for the development of new methods for treating patients using cell therapy. Positive results of transplantation of autologous MSCs for the correction of defects in the integumentary tissues of the human body are reported in the publications of many specialists [27–30]. In particular, the regenerative potential of VT SCs is clearly demonstrated in cases of VT transplantation to correct soft tissue defects. The transferred autologous tissue contains many cells, including SCs, which ensure neovascularization of the injected AT due to the secretion of angiogenic growth factors [11, 31, 32].





Results of the use of MSCs from AVT in plastic and reconstructive surgery of the mammary glands

Correction of congenital breast deformities, consequences of surgical treatment of patients with breast cancer (BC), as well as mammoplasty for aesthetic reasons are the most common operations performed by plastic surgeons. In these cases, along with endoprosthesis of the mammary glands, free autoadipotransplantation - lipofilling (LF) is widely used [33].

The introduction of fat autografts to eliminate deformities of the mammary glands was initially often accompanied by partial necrosis of the adipograft, the formation of calcifications and fatty cysts, which significantly complicated the interpretation of the results of radiological research methods for breast cancer screening [34, 35]. Various ways to improve the survival of autoadipografts have been proposed. The most effective way to solve this problem is considered to be cell-associated lipotransfer, first performed in an animal experiment by D. Matsumoto et al. in 2006 [12]. These authors proposed using an autoadipograft saturated with SA to increase the volume of soft tissues. It is believed that this approach significantly increases the survival rate of transplanted adipocytes, reduces the degree of graft destruction, and reduces the incidence of fibrosis of surrounding tissues and the formation of fatty cysts [12].

A number of authors perform increase in the volume and correction of the shape of the breast using CSL for aesthetic indications [36, 37]. In particular, K. Yoshimura et al. [37] provide data on the positive experience of using CSL for cosmetic reasons in 40 cases of increased breast volume. The authors did not note any complications from this operation. In only one observation, routine magnetic resonance imaging (MRI) after surgery revealed ectopic (parasternal) formation of fibrous tissue. When the authors assessed the long-term results of the operation after 2 years, according to MRI and mammography, they found an increase in the volume of the mammary glands from 100 to 200 ml without any pathological changes in the area of the surgical intervention [37].

For aesthetic reasons, in order to increase the volume of the mammary glands, 20 somatically healthy patients T. Kamakura, K. Ito, 2011 [36], were treated with CSL. To obtain SSF components from aircraft, the authors used a Celution 800 System apparatus (USA). The rate of positive assessment of the results of the operation by patients participating in the study was 69%. When performing MRI in the postoperative period, fatty microcysts formed in 2 (10%) cases, which subsequently calcified. No other negative consequences of using the technique were identified [36].





Based on an analysis of data from a prospective study assessing the effectiveness of CSL in comparison with that when using LF in cases of increasing the volume of the mammary glands for aesthetic indications for surgery, H. H. Peltoniemi et al. [38] concluded that performing CSL has no advantages over traditional LF, provided that water-jet liposuction is used to collect VT. However, the differences identified by the authors cannot be considered statistically significant. In a group of 18 women whose information was included in the study, in the postoperative period the degree of autoadipograft resorption was monitored by the authors using MRI data. It turned out to be comparable in the study and control groups. The authors concluded that the use of autologous VT transplantation to increase breast volume for aesthetic reasons without enriching the autoadipograft with SC can reduce the duration of surgery and reduce the risk of microbial contamination of the transplanted biological material, and also reduces the overall cost of the operation with comparable treatment results [38].

Currently, the possibilities of using cell therapy options are being explored, in which patients first undergo classical lipofilling to fill soft tissue defects, after which SCs from VT are separately injected into the corrected area. This technique is called “staged cell-linked lipotransfer” – ECL [30].

T. Tiriyaki et al. [30] reported the use of EXL in 29 cases to eliminate soft tissue defects of the human body of various origins and anatomical locations. When implementing EXCL in clinical practice, no complications of surgical intervention were identified in the postoperative period. A significant decrease in the degree of autoadipograft resorption was found compared to traditional lipofilling.

Data from M. Zhu et al. [39] suggest that the use of SC helps to improve the reconstructive properties of transplanted VT, significantly reducing the level of its resorption in the long-term period of observation of patients.

To study the clinical effectiveness of cell-associated lipotransfer, S. F. Kolle et al. [28] undertook a triple-blind randomized controlled trial in which 13 participants received autoadipografts of the same volume (enriched and unenriched SCs from VT) subcutaneously into predetermined areas of the body. When assessing the results of the study, a significant reduction in the degree of fat cell resorption was found in cases of CSL compared with traditional methods of fat tissue transplantation [28].

Specialists in the field of cell therapy have particular hopes for the possibility of using CSL to eliminate breast deformities in patients undergoing





surgery for cancer of these organs. Elimination of breast deformities in patients who have undergone surgical treatment for malignant neoplasms (MNT) gl. mammae is one of the pressing problems of modern oncology, since this approach allows us to accelerate the pace of social rehabilitation and improve the quality of life of women. At the same time, some researchers state that MSCs can increase the risk of metastasis of tumor cells in breast cancer after performing CSL [40, 41]. It is also possible that injections of SA from VT to fill breast defects in patients who have undergone surgical treatment of breast cancer may increase the risk of developing local recurrence of cancer, creating a specific environment at the site of their introduction into the soft tissues that stimulates the resumption of the tumor process against the background of neoangiogenesis [42, 43].

At the same time, other authors come to the conclusion that CSL is an effective and safe surgical intervention, optimal in cases of eliminating breast deformities that occur in patients after glandulae mammae quadrantectomy for cancer, and does not increase the likelihood of breast cancer recurrence after surgery [44]. Currently, in the absence of tumor recurrence in the long-term follow-up period, replacement of breast defects in patients who have undergone surgery for breast cancer can be carried out through LF of this anatomical region [45].

In 2012, breast oncologists undertook a prospective multicenter study "Restore-2", during which data on the results of examination and treatment of 71 patients operated on for breast cancer were analyzed; after surgery, breast deformation occurred in all cases [44]. The main goal of the authors in carrying out the work was to evaluate the reconstructive and aesthetic capabilities of CSL in cases of correction of postoperative deformities of the breast 12 months or more after the initial operation. In the majority (63.4%) of clinical observations, patients assessed the results of surgical correction of breast volume on a 6-point scale with satisfaction ranging from 4 to 6 points. The duration of observation of women who underwent surgery to correct the shape of the breast using CSL exceeded 12 months. When analyzing the study data, the authors came to the conclusion that CSL can be considered an effective and safe option for surgical treatment of patients who need to eliminate breast defects formed after their resection for cancer [46].

Y. Zhou et al. [47] report that the use of CSL in cases of breast tissue reconstruction after surgical treatment for cancer can increase the rate of adipograft engraftment by only 9%, which cannot be considered clinically





significant, and this intervention is associated with an increased risk of complications in the postoperative period, compared to cases of other types of surgical procedures.

Obviously, a promising area of research for specialists in plastic and reconstructive surgery is the search for ways to modernize methods for isolating a culture of MSCs, which could be used in CLS both intraoperatively (as their isolation is completed) and delayed, by selecting SCs from a bank. There is also no doubt that the use of cell technologies in clinical practice should be individually oriented, taking into account the structure of cell populations and the trophic factors they synthesize.

Conclusion

Analysis of data from many researchers allows us to state that, despite targeted scientific work, it is not yet possible to obtain reasoned answers to all questions regarding the use of multipotent SCs from VT in clinical practice. There is no consensus yet on technologies for studying the phenotypic characteristics of SCs from VT, as well as on a universal method for their isolation from the human body. Unanswered questions still remain regarding the assessment of long-term results of cell-linked lipotransfer in areas of excision of breast malignant tumors. The mechanisms of action of stem cells on the body (paracrine or due to differentiation into cells of surrounding tissues) have not been fully studied. Undoubtedly, understanding the depth of the controversial problems of modern treatment of patients with breast cancer using cellular technologies will allow us to more clearly formulate the tasks of upcoming scientific research in terms of assessing the results of using these techniques in surgical practice, including from the perspective of the plastic and reconstructive component of the activities of specialists. With overcoming the problems of developing cell therapy, it will probably be possible to achieve new horizons in regenerative medicine.

Conflict of interest

The authors declared no potential conflict of interest.

conflict of interest statement

Authors declare no conflict of interest.

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