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Possibilities of Using Transplantation of Autologous Adipose Tissue Enriched with Stem Cells in Mammoplasty

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Abstract:

Every year, the number of cases of mammoplasty performed for cosmetic indications increases. However, breast surgeries are often performed for more than just aesthetic reasons. The trend of increasing incidence of breast cancer in women continues [1–3]. Among the technologies of combined treatment of patients with breast cancer, the surgical method remains fundamental. At the same time, both radical mastectomy and partial resections gl.mammae after surgery, it is 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 possibilities of their speedy social adaptation [4].

Introduction

Autologous adipose tissue (AHT) is a unique plastic material used to eliminate soft tissue defects of various anatomical localizations. The experience of using AZT for these purposes is given in the classic works of G. Neuber [5] and E. Lexer [6]. However, it was only the development of technologies for the isolation of mesenchymal stem cells (MSCs) from human AVT that made it possible to consider the possibilities of fat tissue transplantation (VT) in a new light, using the principles of regenerative medicine [7–10]. Stem cells from AVT are similar in cytological properties to stem cells of the bone marrow, and the possibilities of their application are wider due to the relative simplicity of isolation [9, 11].

The sources of scientific literature provide information on cases of transplantation of AWT enriched with KS to correct the shape and volume of the mammary glands both for aesthetic indications and in cases of elimination of postoperative deformities. However, the results presented by the authors of these publications are mixed. The need for a comprehensive assessment of the experience of using SCs from VT in plastic and reconstructive surgery of the breast is the motivation for a special study of materials on this topic.

Material and Methods of Research

Databases https://www.ncbi.nlm were used to collect scientific medical information. nih.gov/pubmed, http://www.cochranelibrary.com/. The information contained in 985 sources of literature published in the period from 2008 to 2017 was studied, among which the content of 47 publications was analyzed purely on the topic of research.

Results of the study and their discussion

On the methods of obtaining MSCs from AZT. Cytological features and possibilities of using stem cells as an autologous material to eliminate soft tissue deformities The main method for improving the results of autoadipotransplantation is considered by many authors to be cell-bound lipotransfer (CSL), proposed by D. Matsumoto et al. in 2006 [12]. Researchers believe this because this technology involves the enrichment of transplanted adipose tissue with MSCs. In this regard, the search for optimal Ways of obtaining VT for isolation of MSC culture seems to be one of the significant directions in the study of the possibilities of using this type of cell material in clinical practice [13–15]. Some researchers report positive results of VT collection during vacuum aspiration from donor sites of the human body [16]. Other authors believe that VT for isolation of MSC culture is best obtained through lipoectomy [17]. A number of experts are convinced that the method of VT sampling does not significantly affect the amount of SCs isolated from it [18].

N. Gnanasegaran et al. [15] showed that the levels of gene expression and the potency of stem cells from VT to a certain differentiation are determined by the method of obtaining tissue material during liposuction/lipoectomy.

After the preparation of the AZT, the SC culture is isolated from it. The most common method of isolation of stem cells from VT is considered to be the enzymatic cleavage of lipoaspirate (LA) into cells of the stromal vascular fraction (SSF), which contains stem, stromal and endothelial cell elements, pericytes, leukocytes, erythrocytes and a number of non-cellular byproducts [19]. Dyspase, trypsin, but most often collagenase are used for fermentation of VT. First, the aircraft is washed with a sterile solution of phosphate buffer until the substrate is golden brown, 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 bottom layer is transferred to tubes and centrifuged. The precipitate consists of SSF cells, which are resuspended in control media, counted, and placed in individual flasks with a concentration within 1×106 cells. In general, more than 1×107 SSF cells are obtained from 20 mg of lipoaspirate [14].

The possibility of isolation of SCLT from LA by non-enzymatic methods is based on the fact that after the drug stem cells are located at the bottom of the aspiration tank. Cells isolated by non-enzymatic methods do not differ phenotypically and in their ability to differentiate from similar cells obtained during LA fermentation, but their number is 19–20 times lower in the end [14, 20, 21].

In 2006, the International Society for Cell Therapy (IOCT) defined a set of cytological criteria for the identification of SC VT [22]. It includes plastic adhesiveness under standard cultivation conditions; CD73, CD90 and CD105 expression; lack of expression of CD45, CD34, CD14 or CD11b, CD19 or CD79α and HLA-DR surface molecules [22]. In 2013, additional positive markers (CD13, CD29, and CD44) were identified by MOCT on the surface

SC VT in more than 80% of cases, and CD31, CD45, and CD235a were regarded as the main negative markers, as they were found on the surface of SCT in less than 2% of cases [19]. In order to phenotype cells as mesenchymal multipotent, at least two positive and two negative markers must be present on the surface of the stem cells, and the viability of the cell elements must exceed 70%. In addition, isolated stem cells must necessarily have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts [23].

In general, the main features of SCs are their relative simplicity of obtaining with minimal surgical traumatization of 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 VT stem cells are characterized by more pronounced proliferation and cultivation capabilities compared to bone marrow stem cells [24–26]. The ability of SC VT to differentiate not only into adipocytes, but also into osteoblasts, chondrocytes, myocytes, epithelial cells and neurons, makes it potentially possible to use them for the restoration of many tissues of the human body [7].

The identification of the unique ability of stem cells from VT to regenerate, secrete trophic factors and differentiate into various cell types turned out to be a prerequisite for the development of new methods of 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 have been reported in the publications of many specialists [27–30]. In particular, the regenerative potential of VT SCs is clearly demonstrated in cases of AVT transplantation to eliminate soft tissue defects. The relocated autologous tissue contains many cells, including stem cells, that provide neovascularization of injected VT due to the secretion of angiogenic growth factors [11, 31, 32].

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

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

The introduction of fat autografts to eliminate mammary gland deformities was initially often accompanied by partial necrosis of the adipograft, the formation of calcifications and fat cysts, which significantly complicated the interpretation of the results of radiation examination methods during breast cancer screening [34, 35]. Various ways to increase the survival rate of autoadipografts have been proposed. The most effective way to solve this problem is considered to be cell-coupled lipotransfer, first performed in an animal experiment by D. Matsumoto et al.

in 2006 [12]. These authors suggested the use of a KS-saturated autoadipograft 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].

An increase in the volume and correction of the shape of the breast with the use of CSL are performed by a number of authors 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 of this operation. Only one case of 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, MRI and mammography revealed 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, 20 somatically healthy patients T. Kamakura and K. Ito, 2011 [36] used CSL to increase the volume of the mammary glands. To obtain SSF components from aircraft, the authors used the Celution 800 System (USA). The rate of positive evaluation of the results of surgery by patients participating in the study was 69%. During the MRI scan in the postoperative period, fatty microcysts formed in 2 (10%) cases, which subsequently calcified. No other negative effects of the technique have been identified [36].

Based on the analysis of data from a prospective study to evaluate the efficacy of CSL in comparison with that of LF in cases of breast enlargement due to aesthetic indications for surgery, H. H. Peltoniemi et al. [38] concluded that the performance of CSL has no advantages compared to 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 the group of 18 women included in the study, the degree of autoadipograft resorption was controlled by the authors using MRI data in the postoperative period. It was found to be comparable in the study and control groups. The authors concluded that the use of autologous VT transplantation to increase the volume of breast cancer for aesthetic indications without enrichment of the KS autoadipograft can reduce the duration of surgical intervention and reduce the risk of microbial contamination of the transplanted biological material, as well as reduce the overall cost of surgery with comparable treatment results [38].

Currently, the possibilities of using cell therapy options are being investigated, in which patients first undergo classical lipofilling to compensate for soft tissue defects, after which SCs from VT are separately injected into the corrected site. This technique is called "staged cell-coupled lipotransfer" (ECL) [30].

T. Tiryaki et al. [30] reported the use of ECL in 29 cases to eliminate defects in the soft tissues of the human body of various genesis and anatomical localization. During the implementation of ECL in clinical practice, no complications of surgical intervention in the postoperative period were revealed. A significant decrease in the degree of autoadipograft resorption compared to traditional lipofilling was established.

The data of M. Zhu et al. [39] suggest that the use of stem cells improves the reconstructive properties of the transplanted VT, significantly reducing the level of its resorption in the long-term follow-up period of patients.

To study the clinical efficacy of cell-bound lipotransfer, S. F. Kolle et al. [28] undertook a triple-blind randomized controlled trial, during which 13 participants were injected with autoadipografts of the same volume (enriched and unenriched stem cells from VT) into predetermined areas of the body under the skin. When evaluating the results of the study, a significant decrease in the degree of fat cell resorption was found in cases of CSL compared to traditional methods of adipose tissue transplantation [28].

Specialists in the field of cell therapy are especially hopeful about the possibility of using CSL to eliminate breast deformities in patients operated on for cancer of these organs. Elimination of breast deformities in patients who have undergone surgical treatment for malignant neoplasms (malignant neoplasms) gl. *mammae* is one of the urgent problems of modern oncology, since this approach makes it possible to accelerate the pace of social rehabilitation and improve the quality of life of women. At the Some researchers state that MSCs may increase the risk of tumor cell metastasis in breast cancer after CSL [40, 41]. It is also possible that injections of stem cells from VT to compensate for breast defects in patients who have undergone surgical treatment of breast cancer may increase the risk of local recurrence of malignant neoplasms by creating a specific environment at the locus of their injection into soft tissues that stimulates the resumption of the tumor process against the background of neoangiogenesis [42, 43].

At the same time, other authors conclude that CSL is an effective and safe surgical intervention that is optimal in cases of elimination of breast deformities that occur in patients after a quadrantectomy of *glandulae mammae* for cancer, and does not increase the likelihood of breast cancer recurrence after surgery [44]. At present, in the absence of tumor recurrence in the long-term observation period, the replacement of breast defects in patients who have undergone surgery for breast cancer, can be performed by means of LF of this anatomical region [45].

In 2012, breast oncologists undertook a prospective multicenter study called Restore-2, which analyzed data on the results of examination and treatment of 71 patients operated on for breast cancer, after surgery in all cases there was a deformation of the breast [44]. The main goal of the authors was to assess the reconstructive and aesthetic capabilities of CSL in cases of correction of postoperative deformities of the breast 12 or more months after the primary surgery. In the majority (63.4%) of clinical cases, patients assessed the results of surgical correction of the volume of the mammary glands on a 6-point scale with satisfaction in the range from 4 to 6 points. The duration of follow-up for women who underwent breast correction surgery with the use of CSL exceeded 12 months. When analyzing the study data, the authors concluded that CSL can be considered an effective and safe option for surgical treatment of patients when it is necessary 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 malignant neoplasms can increase the engraftment rate of adipografts by only 9%, which cannot be considered clinically significant, and the performance of this intervention is associated with an increased risk of complications in the postoperative period, compared to cases of other types of surgical aids.

Obviously, a promising area of research for specialists in plastic and reconstructive surgery is the search for ways to modernize the methods of isolation of MSCs culture, which could be used in CSPs both intraoperatively (as their isolation is completed) and delayed, by selecting SCs from the 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 synthesized by them.

Conclusion

The analysis of the data of many researchers allows us to state that, despite the purposeful scientific work, it is not yet possible to obtain reasoned answers to all questions regarding the use of multipotent stem cells from VT in clinical practice. There is no consensus yet on the technologies for studying the phenotypic characteristics of stem cells from VT, as well as on the universal method of their isolation from the human body. The questions of assessing the long-term results of cell-coupled lipotransfer in the areas of excision of malignant neoplasms of the breast still remain unanswered. The mechanisms of stem cells' influence on the body (paracrine or due to differentiation into cells of surrounding tissues) are not fully understood. Undoubtedly, understanding the depth of controversial problems of modern treatment of breast cancer patients with the use of cell technologies will allow us to more clearly formulate the tasks of the upcoming scientific research in terms of assessing the results of the use of these techniques in surgical practice, including from the perspective of the plastic and reconstructive component of the activities of specialists. With the overcoming of the problems of the formation of cell therapy, it is likely that it will be possible to reach new horizons in regenerative medicine.

Conflict of Interest

The authors stated that there was no potential conflict of interest.

conflict of interest statement

Authors declare no conflict of interest.

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