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Potential of Adipose Tissue Derived Stem Cells in Scaffold Assisted Breast Reconstruction

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Keywords: Breast cancer; Breast reconstruction; Adiposed-derived stem cells (ADSC); Scaffold.

Abstract

Objective: To provide a simple explanation regarding the utilization of ADSCs in tissue engineering and their use for breast reconstruction.

Methods: Literature searches were performed on April 6 and April 10, 2021 on Google Scholar, using keywords: 'breast cancer' and 'adipose stem cells'. Data were analyzed and presented descriptively in the form of text and figures.

Results: One of the various methods of breast reconstruction is to use a tissue engineering approach by using Adipose Tissue Derived Stem Cells (ADSC) and a three-dimensional scaffold. Therefore, we discussed about stem cells, ADSCs, the use of ADSCs and scaffolds in breast tissue engineering, and safety of ADSCs usage in scaffold assisted breast reconstruction.

Conclusion: Reconstruction procedures using ADSC must be under close supervision and continuous evaluation, both in terms of short-term and long-term safety in order to maintain continuity and quality of life of breast cancer patients.

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Introduction

Breast cancer is one of the most common malignancies in women [1], the incidence of breast cancer covers about 25% of all cancer cases in women annually. The high incidence of breast cancer was the cause of 570,000 deaths in 2015 [2]. Various methods have been developed to increase the cure for breast cancer; thus in America there has been an increase in breast cancer cure rate of up to 90% [3]. Various treatments are available to treat breast cancer. Mastectomy is one of the treatments that is performed on approximately 40% of breast cancer patients, but the procedure has a negative effect on aesthetics appearance and psychosocial condition of patients [4,5]. Therefore, breast reconstruction is an option to deal with the negative effects of mastectomy, which is expected to improve patient's quality of life [6].

Breast reconstruction can be done by several methods, such as plastic surgery, administration of the platelet growth factor, breast implants, cell-based therapies and tissue engineering [1,7]. Reconstructive procedures continue to be developed to meet patient needs and optimize results, one of the emerging approaches in tissue engineering for breast reconstruction is breast adipose tissue engineering [8]. For that purpose, Adipose Tissue-Derived Stem Cells (ADSCs) are used [9]. Reconstruction using ADSCs is very interesting because they provide the potential for adipocyte proliferation, differentiation, and maintenance of fat volume [5]. Therefore, it is very important to gather information regarding ADSCs and their use in the application of tissue engineering for breast reconstruction. Sufficient information is expected to make it easier to understand tissue-engineering technology from the basic concepts, as well as its safety to be applied in breast reconstruction. Therefore, the purpose of this article was to provide a simple explanation regarding the utilization of ADSCs in tissue engineering and their use for breast reconstruction, and we discussed about stem cells, ADSCs, the use of ADSCs and scaffolds in breast tissue engineering, and safety of ADSCs usage in scaffold assisted breast reconstruction.

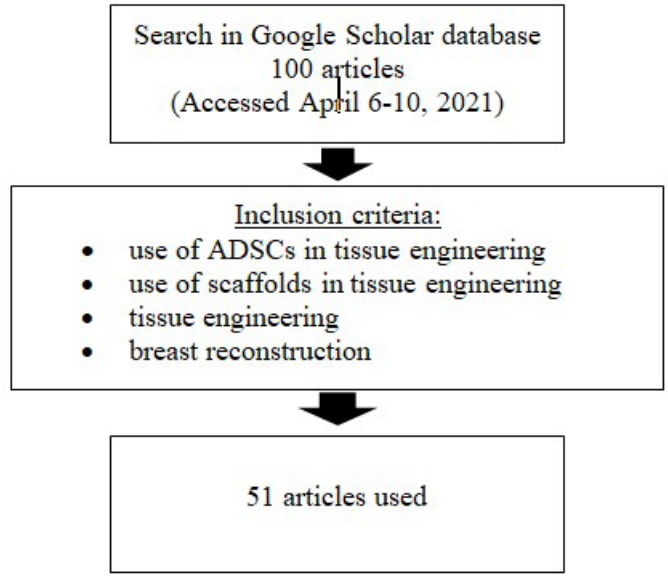

Figure 1: The search flow and article selection.

Methods

Literature searches were performed on April 6 and April 10, 2021 on Google Scholar, using keywords: 'breast cancer' and 'adipose stem cells'. Inclusion criteria: articles in English, which addressed stem cells, use of ADSCs and scaffold in tissue engineering, and their benefits in the application of breast reconstruction procedures. Data were analyzed and presented descriptively in the form of text and figures.

Results & discussion

From the search results, we obtained 100 articles, and after screening, we used 51 articles to write this review article. **Stem cell**

Cell is the smallest structural and functional unit of living things. A total of 230 cell types are found in the human body, and each cell has its own uniqueness by function [10]. Stem cells are cells that have the potential to differentiate into other type of cells with specific functions. Not only can differentiate into other cells, stem cells also have the ability to regenerate by way of cleavage [11].

Stem cells may come from various sources; therefore, stem cells are divided into several types, namely adult stem cells, fetal stem cells, embryonic stem cells, and extraembryonic stem cells. Adult stem cells are also known as somatic stem cells. Somatic stem cells multiply and differentiate into different types of cells that are parts of tissues or organs. These types of stem cells are multipotent and play a role in maintaining and repairing the tissues where the stem cells are found, and one type of them are ADSCs [12].

Adipose tissue-derived stem cells (ADSC)

In the latest development, ADSC is known to have good differentiation ability into cells that are adipogenic, osteogenic, chondrogenic, myogenic, neurogenic, endothelial, hepatic, and can even differentiate into endocrine cells such as pancreatic cells so that they can secrete insulin. These abilities of ADSCs are known to give promising results in in vivo studies [13-16], thus ADSCs are often used in tissue engineering.

ADSCs belong to the type of somatic stem cells that are located in adipose tissue [17]. These cells can secrete various growth factors that may provide a great effect on vascular growth, migration and differentiation of endogenous stem cells. Therefore, fat tissue grafting often uses ADSCs, and it is expected that they give a good effect on clinical outcomes and increase the success of the performed fat grafts [18-20]. In addition, ADSCs various beneficial effects are thought to improve wound healing process, tissue repair, and support good graft resistance [21].

The method used to obtain ADSCs is to extract the Stromal Vascular Fraction (SVF) from fat tissue that can be obtained through liposuction technique [22]. Unlike other mesenchymal stem cell retrieval, which is more invasive or sacrifice an embryo, such as Bone Marrow-Derived Stem Cells (BMSCs) or Embryonic Stem Cells (ESCs), ADSCs do not require invasive retrieval process, and the results of proliferation in cultures are more and last longer than BMSCs [23-26]. The ADSC isolation process involves the use of a collagenase enzyme, then separation of mature adipocytes from the SVF by centrifugation [27]. The best cell propagation media for cell therapy purposes is one with xeno-free material in order to reduce the possibility of virus transmission and immune reactions [28]. ADSCs might be used as cell sources in tissue engineering, and for this pur-

pose, a scaffold that is suitable to engineer a particular tissue is needed, so that cells can differentiate according to the desired shape and three-dimensional design of the tissue.

The process of isolation and implantation of adipose tissue stem cells can be seen in Figure 2 that shows the flow of adipose tissue stem cell isolation from sample collection to implantation. This method was chosen because it was relatively safe with a relatively low complication rate [29]. Sampling was carried out at superficial abdominal area, as this area is known to have adipose stem cells that are more resistant to damage or cell death than other areas such as the upper arm and mid-thigh [23]. Lipoaspirate, which was obtained from liposuction procedures, was immediately rinsed in 1% Bovine Serum Albumin (BSA) or Phosphate-Buffered Saline (PBS) [30]. Clean fat tissue was then processed using collagenase to destroy the extracellular matrix at 37°C for 1 hour, after which the centrifugation process was carried out to obtain SVF [16,29].

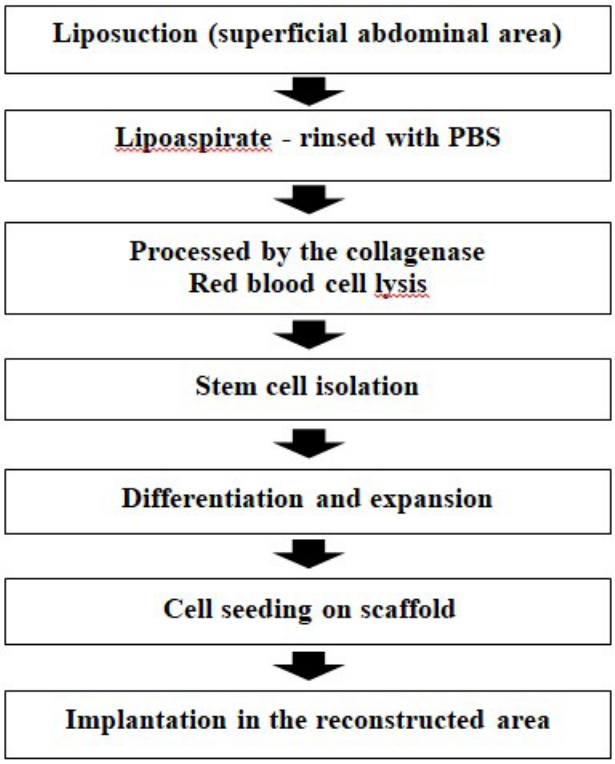

Figure 2: Adipose tissue stem cell isolation and implantation protocol.

In SVF, ADSCs can be distinguished from mature adipocytes, as mature adipocytes contain lipid droplets, while ADSCs after culture have a fibroblast-like morphology [5]. ADSC isolation can be done by culturing under standard conditions in 10% Fetal Bovine Serum (FBS) containing medium in a plastic tissue culture flask, and ADSCs will grow into a mono layer [23,29]. Expansion of cultured cells takes about 2-4 days [15].

The use ADSC and scaffold in breast tissue engineering

Tissues and organs have complex characteristics so that tissue/organ engineering requires complex and comprehensive control of cellular and intracellular mechanisms. Therefore, tissue/organ engineering requires certain requirements that must pay attention to several important aspects such as genetics, molecular and cellular conditions based on the characteristics and needs of the engineered tissues or organs. Breast tissue is composed mostly of glandular and adipose tissue, therefore adipose tissue engineering is appropriate for breast reconstruction. In addition, bioartificial printing technology might be required in adipose tissue engineering [31].

In adipose tissue engineering, the implantation of ADSCs on scaffold is preceded by decontamination of the scaffold using ultraviolet light for 1 hour, followed by rinsing the scaffold using 70% ethanol, and incubation in 10% FBS containing DMEM overnight. ADSCs are seeded on the scaffold and incubated in 10% FBS containing DMEM for 2 hours so that the cells are well embedded on the surface of the scaffold, and then the scaffold can be implanted in the area to be reconstructed [14].

Another method that can be done is to first implant the scaffold in the reconstruction area; this process will cause the formation of blood clots in the scaffold structure [32]. The purpose of the process is to stimulate the formation of a fibrin network, which is an initial response that is needed in the formation of new blood vessels, so that subsequent injection of adipose cells on the scaffold can be performed after 14 days of scaffold implantation [33].

The use of scaffolds in adipose tissue engineering and implantation is required to stimulate cell production and proliferation. Scaffold construction might be designed in three and two dimensions. In addition, the selection of the right scaffold material is also important, in order to avoid problems such as volume retention and to fulfil the need of vascularization [26]. Scaffolds are made in such a way as to resemble the shape of the tissue in vivo so as to produce suitable tissue in the transplant area [34]. There are mainly 2 types of scaffold materials, natural or biological and synthetic. Biological scaffolds consist of collagen, gelatine, silk and alginate materials [35-40]. Synthetic materials, which can be used as scaffolds, are Polyglycolic Acid (PGLA), Polyethylene Glycol (PEG), Polycaprolactone (PCL) and Poly-L-Lactic Acid (PLA) [41,42].

Adipose tissue engineering using scaffold is a technique to overcome tissue damage in large volume reconstruction. In its application, a scaffold is used as a substrate to provide a direction for growth of cells that is needed in tissue regeneration, so it is hoped that it can help to provide precise growth control and topography to obtain good regeneration results [43,44]. At the cellular level, scaffolds may promote adipogenesis through substrates that provide a texture that matches the original tissue [45]. Moreover, scaffolds may provide space and support for cell growth and fat tissue formation, which is important to reduce mechanical stress, as high mechanical stress on fat tissue may inhibit the formation of new fat tissue [46,47].

Previous research conducted by Chhaya et al., regarding the use of scaffolds for tissue regeneration showed the formation of fat tissue that was well organized with blood vessels and in accordance with the volume and thickness of the scaffold [33].

Safety of ADSC usage in tissue engineering practice

The benefits of ADSC's in breast reconstruction have been widely recognized, but in terms of safety, there are still concerns in long-term effects. One of the concerns is the ability of ADSCs to stimulate cell growth and angiogenesis. In case of a cancer survivor, ADSCs may trigger the remnants of cancer cells to grow back [48]. However, studies showed that ADSCs only promoted the growth of active breast cancer cells and did not reactivate dormant residual cancer stem cells [49,50]. In addition to these concerns, other possible complications that should be considered are adipose tissue necrosis, impaired graft success, and volume loss [51].

Conclusion

ADSCs and a planned scaffold design have potentials in breast reconstruction to restore the aesthetics, volume and shape of the breast. Reconstruction procedures using ADSC must be under close supervision and continuous evaluation, both in terms of short-term and long-term safety in order to maintain continuity and quality of life of breast cancer patients.

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