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Role of autologous fat graft in the treatment of radiotherapy toxicity

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Abstract

According to the recent information, it was revealed that adipose tissue derived mesenchymal stem cells have ability to turn into proliferation and differentiation cells. As a result, in the treatment of many disorders such as cleft lip and cleft palate, burn scars, progressive hemifacial atrophy, myocardial infarction, spinal cord injuries, neurological deficits and many congenital or post-traumatic defects, autogene fat graft has been started to use. With successful results of clinical and experimental publications, new projects have been put together exponentially.

Adipose tissue derived stem cells were reported to either reduce or prevent RT related toxicity with angiogenic, anti-apoptotic and multipotent cellular activity properties. Today, in the treatment of radiation induced toxicity, autologous fat grafting has also been started to use. However irritated tissue is counted as ischemic, either to what extent fat cells in these tissues differentiate or how they are affected are not known. Despite current use of fat graft to reduce complications, further studies examining fat graft viability under radiation therapy are needed.

Introduction

Adipose tissue is a special type of connective tissue rich in blood supply developed from embryonic mesoderm and made of adipocytes. While it takes metabolically active place in steroid production, thermoregulation, fluid and electrolyte homeostasis, it is also important in maintaining the structural support and prevention of vital organs. Distribution of fatty tissue to the body parts varies according to subcutaneous thickness, age and gender. A person with normal weight, adipose tissue makes 15-20% of body weight in men; in women it constitutes 20-25%. It is located intensively under the abdominal skin, at buttocks, axilla and thighs. Subcutaneous adipose tissue plays a major role in shaping the body surface [1-4].

According to the published reports, besides adipocytes, fat tissue contains preadipocytes, fibroblasts, smooth muscle, endothelial and multipotent fat derived stem cells [5,6]. In particular, foundation of amount of mesenchymal stem cells in the fat tissue 500 times more than the bone marrow has given a new scientific dimension [5]. As a result of either in vivo or in vitro assays, adipose tissue derives stem cells have been proved to transform into blood vessels, cartilage, bone, muscle and nerves. Although pathogenesis hasn't been fully understood stem cells are known for role in repair of minor damage, angiogenesis stimulation. Also, they turn into different types of cells when needed, inhibits apoptosis and promotes synthesis of factors for regeneration. It has been shown that by differentiating to endothelial cells and inducing synthesis of growth factors such as VEGF, FGF, TGF-β and HGF, they increase neovascularization [5,6-12].

Ease of autogene fat tissue obtaining, lack of tissue compatibility, unlikeliness to lead antigenic or allergic reactions, donor sites adequacy and variety, low morbidity, rapid availability, large stem cell content and when needed plentiful is available make it preferable in the latest clinical trials. In addition to these advantages, when liposuction is performed, scar doesn't occur in the donor area, and long-term changes in volume and contours are ensured [3,5,13-16]. The adventure of fat graft started with aesthetic purposes, with the concept of stem cell, has begun to have place in many areas of medicine in the daily practice. Upon reviewing the literature of the last 100 years, autologous fat injection has been performed successfully in orthopaedics, neurosurgery, general surgery and plastic surgery to fix many congenital or post- traumatic defects such as nerve closure, ocular enucleation, cleft lip and cleft palate repair, treatment of acne scars, sequels due to facial nerve paralysis, covering bone defects, progressive hemifacial atrophy, bilateral lipoatrophy, to fill the atrophic areas after steroid injections and mastoid defects. However, in the long run because the volume change rate was between 20-80%, usage of autogene fat graft has been stayed limited [17-25].

In the last 20 years, studies have shown that fat graft when applied in appropriate amount and injected intramuscular or peri muscular resulted in good results. In the first year after grafting, the loss was reported to be of 45%. Around 2 years later, it was found that even 50% of the graft was viable. In addition, in case of weight gain after revascularization, it was observed that grafted fat tissue was affected and increased its volume. Both because of this and long contour recovery time after fat injection is an expected condition [9,24-28].

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Using fat graft in radiotherapy related complications

Nowadays, with understanding malignant cells' reaction to radiation, it has been started being used proportional to technological capabilities to treat many cancers. Radiotherapy is used in intend to create DNA damage in tumour cells. However, as a result of irradiation of non-tumour tissue, acute and chronic side effects can be observed. In tissue exposed to radiation, endothelial apoptosis or delayed mitotic tissue death occur. If mitotic cells are fibroblasts, they differ into fibrocytes and store collagen intensively. If they are in form of capillary structure, progressive loss and fibrosis occur. In tunica media of arteriolar structure, significant reduction occurs in tissue perfusion with progressive fibrosis. Shortly, in the remaining organs exposed to radiation, in addition to parenchymal cell injury, significant changes occur in vascular endothelial cells, capillaries and fibroblasts and these pathological changes cause chronic radiation damage [29-32].

In both animal and human studies, after autologous fat injection quality of fat tissue was found to increase at the injection site and this result brought use of fat grafting for radiation related toxicity. Mesenchymal stem cells found in adipose tissue have been shown to decrease radiotherapy related complications by turning into cells those serve to wound healing and epithelization, growth hormone secretion, cytokines and angiogenic factor secretion, increase in collagen production, reduce collagen disorganization, with improved skin quality [6,7,11,16,26].

By damaging DNA, radiation harms healthy cells. Mesenchymal stem cells increase release of antioxidant enzymes by inducing dermal fibroblasts and keratinocytes. Furthermore, as well as stem cells in the fat tissue secrete subtypes of superoxide-dismutase to protect cells against oxidants [10]. In the many published studies after fat tissue injection connective-vascular tissue rich in stem cells and increased release of angiogenic factors were observed. This release resulted in an increase in micro vessels and as a result altered circulation was repaired eventually. These sequential events are based on mesenchymal tissue formation or repair that include stem cell invasion of the damaged area, secretion of angiogenic factors, neovascularization and consequently oxygenation [12,16,26,33]. Stem cells in adipose tissue was shown to increase secondary wound healing by using scaffold consisting of acellular dermal matrix [34].

According to wound model created in rats, fat tissue cultured in a hypoxic environment was observed to get smaller 27% more than fat tissue cultured in a normoxic environment. At last, it was reported that stem cells in fat tissue showed more capacity to proliferate in hypoxic conditions [35]. Luan et al gave adjuvant radiotherapy to the scalp of rats and injected human fat graft to subcutaneous tissue. Irritated and non-irritated tissue was compared, and they found increased dermal thickness, collagen deposition and vascularity in the irradiated tissue [33]. Considering the irradiated tissue and its surroundings, hypoxic, hypocellular and hypo vascular environment occurs and given features of mesenchymal stem cells, they are beneficial in the wound healing process in multiple stages [34-36]. This curative effect of the fat tissue is connected to presence of high proportion of stem cells in the adipose tissue.

Chronic radiodermatitis and radio dermo necrosis of healthy skin and subcutaneous soft tissue are the limiting factors for radiation oncologist. Also, for plastic surgeons it appears to be a serious problem to be solved in the post-treatment period. When the literature is searched, there are some studies with good results wherein fat grafts were used to prevent or reduce late time side effects of radiation and implants [38-42]. Today fat grafts have been used to treat post-radiation effects on skin and subcutaneous tissue. Injection of adipose tissue to the breast has been used in breast cancer patients during breast reconstruction and lumpectomy. And in cases of revision autologous tissues are used for reconstruction. In clinical practice, many breast cancer patients apply to the clinics mostly after radiotherapy for reconstruction. In plastic surgery especially after the surgical treatment of breast cancer, prosthetic techniques, various autologous flaps or combinations of both are performed for breast reconstruction. Particularly breast reconstructions following adjuvant radiotherapy have less success rates due to adverse effects of radiotherapy [43-49]. There are reports showing reduced complications rates with use of fat grafts before and after breast reconstruction with prosthesis in patients received radiotherapy after lumpectomy or mastectomy.

With that, in patients receiving radiotherapy after fat grafting, local complications such as fat necrosis, infection can be seen more [32-50]. It was reported that adipocytes may had paracrine and endocrine interactions with tumour cells and stromal elements [51]. The fat grafts used in breast cancer were thought to cause local recurrence, distant metastasis or development of new cancers; there was no relationship in the clinical series. There is aromatase activity in the adipose tissue. Thus, fat tissue is the main source of post-menopausal oestrogen hormone. Tumour cells and surrounding tissue were found to be higher in aromatase activity. Therefore, when fat tissue is injected subcutaneous or under the gland rather than into the parenchyma local recurrence risk is low [18]. When fat tissue is injected to breast, a good physical examination and mammography should be performed. After fat injection, sometimes calcifications are formed as a result of undergoing necrosis and they interfere with malignancy. Therefore, before and after the procedure, mammography must be taken for comparison and existing and or newly developed calcifications should be determined [36]. Rigotti et al used purified autologous lipoaspirates in breast cancer patients with late term complications of radiation therapy and observed increase in neovascularization and wound healing [18]. Panettiere and colleagues compared aesthetic and functional features of fat grafts in radiotherapy received breast cancer patients and control group. In the fat graft group, all clinical symptoms and aesthetic scores were significantly higher than the control group [32].

Conclusion

Mesenchymal stem calls in adipose tissue and organs play role in repair of minor injuries. Also, they turn into different cell types, inhibits apoptosis and are stimulant for factors needed for regeneration. Although they were shown to be beneficial for radiation related wound healing and other regenerative applications, in clinical practice they haven't had routine use. Because irradiated tissue is accepted as ischemic, fat graft survival in these areas may be expected to be less when compared to healthy tissue. Prospective clinical studies observing fat graft survival in patients receiving radiotherapy need to be explanatory.

Conflicts of interest

The authors declared that there is no conflict of interest.

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