

CELL-POTENTIATED REGENERATIVE TECHNOLOGIES FOR RESTORING JAW BONE TISSUES IN CASE OF ODONTOGENIC INFLAMMATORY & DESTRUCTIVE PROCESS

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ABSTRACT — The study offers a view on the results of comparing conventional and advanced innovation-based cell-potentiated methods used to restore jaw bone tissue in case of odontogenic inflammatory & destructive process. The source of regenerative cells and stimuli was autologous stromal vascular fraction of adipose tissue (SVF-AT). The study involved 158 patients with moderate and severe periodontitis; 112 patients with odontogenic cystic formations. Using SVF-AT through directed regeneration of periodontal tissues (n = 95) improved significantly the clinical, functional and aesthetic outcomes of the treatment, ensuring a higher increase in clinical attachment (5.66 ± 0.02 vs 3.27 ± 0.03 mm, $p < 0.001$) with a more complete and stable restoration of the support function, and a minimal residual recession of the gingival margin, if compared with the conventional treatment in the control group (n = 63). In maxillary defects osteoplasty, the removal of odontogenic cystic formations in the experimental group (58 interventions) was accompanied with complications less frequently (1.7% vs. 23.9%, $p < 0.001$), while positive clinical outcomes with no recurring inflammatory & destructive processes were twice as common through the long-term observation period (96.6% versus 47.8%, $p < 0.001$) against the control (67 interventions). The morphological assessment outcomes suggest significant inducing effect that SVF-AT works on reparative osteohistogenesis, evidence to that being multiple tissue remodeling sites with a higher density of microvessels and newly developed bone tissue in the biopsy obtained from the experimental group patients if compared to the control. Therefore, the newly developed cell-potentiated methods increase significantly the effectiveness of the treatment offered to patients with odontogenic jaw destruction.

KEYWORDS — stromal vascular fraction of adipose tissue, directed periodontal tissue regeneration, in situ bone tissue engineering, restorative dental surgery

INTRODUCTION

One of the promising areas for developing restorative dental surgery and maxillofacial surgery is the introduction of regenerative and tissue engineering technologies using stem or stromal cells. However, there are a number of objective reasons that impede the use of cell lines obtained outside the human body in practical healthcare, including certain biosafety issues. Stromal vascular fraction of adipose tissue (SVF-AT) is a heterogeneous set of native cells and is considered as a promising multifunctional regenerative resource for clinical use [1, 2]. The composition of SVF-AT includes multipotent mesenchymal stromal cells (MMSC-AT) (1.5% to 25% of the total number of nucleated cells), smooth muscle and endothelial vascular cells, macrophages and lymphocytes [3, 4]. A wide spectrum of angiogenic, anti-inflammatory, immunomodulatory cytokines and growth factors secreted by SVF-AT cells has been described [5]. Attempts are being made to replace cranial-maxillofacial bone defects with tissue-engineering structures, including the MMSC-AT culture and/or the newly isolated SVF-AT [6-9]. However, single and isolated observations presented in the respective literature do not allow evaluating the effectiveness and safety of using SVF-AT in maxillofacial surgery and dentistry.

Aim of study:

to evaluate the effectiveness of the newly introduced cell-potentiated ways to restore bone in dental odontogenic inflammatory & destructive diseases.

MATERIALS AND METHODS

The study implied observing 270 patients with different jaw bone tissue issues of various topography and volume, including 158 patients with moderate to severe periodontitis (Group 1, G1); 112 patients with odontogenic cystic formations (Group 2, G2). Depending on the SVF-AT use in each group, two representative comparison subgroups were identified – the control subgroup (CS) with conventional surgical treatment methods, and the experimental subgroup (ES) where the treatment involved the use of autologous SVF-AT. All the patients underwent examina-

tion, had no concomitant somatic diseases that might affect the treatment outcomes, and signed a voluntary informed consent to join the study. Table 1 offers a general view on the clinical material specifics.

In case of chronic periodontitis (G1), the access and treatment of periodontal pockets were performed through the standard technique for directed periodontal tissue regeneration (DPTR). The sanitized

Table 1. General specifics of the clinical material

Group and type of surgery	Age, min-max, Me	Distribution by gender, female / male	Control subgroup	Test Subgroup
Group 1. Directional regeneration of periodontal tissues	28-60, 42	83/75	63	95
Group 2. Cystectomy with osteoplasty of the maxillary defect	20-69, 52	44/68	67	58

There were no statistically significant differences identified in terms of the age & gender structure, the initial oral cavity status, the size and topography of the dentomaxillary bone defects between the compared subgroups ($p > 0.05$). The surgical intervention was preceded by a conservative-hygienic phase, including the oral cavity sanitation, the mobile teeth immobilization, the mucogingival disorders elimination, preparing protective temporary orthopedic structures for the surgical treatment and rehabilitation period.

In the Plastic Surgery Department, syringe suction of 40–120 ml of subcutaneous adipose tissue from the hypogastric region of the anterior abdominal wall and lateral parts of the body was performed under local infiltration via tumescent anesthesia. The punctures were covered with aseptic cloths with a compression bandage applied. Within one hour, the patient remained in the hospital under observation. Lipoaspirate in syringes was washed with sterile physiological solution with a wide-spectrum antibiotic added, and delivered to the laboratory along with 10–20 ml of the patient's blood serum. The stromal vascular fraction was isolated in a laboratory meeting all the GMP standard requirements. 40–50 ml of the lipoaspirate were enhanced up to 60 ml with a physiological solution containing collagenase enzyme lyophilisate 50 mg (activity 180–290 units/mg) and placed in a sterile plastic bag. After exposure to a water bath for 20 minutes at 37° C, the suspension was distributed into test tubes and centrifuged for 20 minutes at a speed of 2750–3000 rpm. The upper layer of liquid lipids and floating adipocytes was aspirated, and the supernatant poured off. SVF-AT was collected from the tubes bottom and washed with autologous blood serum. Further on, SVF-AT was resuspended with autologous serum and the composition was analyzed using an automatic cell counter. When delivered from the laboratory to the clinic, the material was accompanied with a passport indicating the number of cells and their viability.

periodontal defects in the experimental subgroup (ESG1) were filled with SVF-AT, in the control subgroup (CSG1) a blood clot from the bone marrow spaces and the vital periodontal ligament were used for the same purpose. In both subgroups with deep and wide bone periodontal defects, a granulated osteoconductor was additionally introduced (Biosit-Elcor, St. Petersburg; Bio-Oss, Switzerland; Bone Ceramic, Switzerland). Isolation of the regeneration site was carried out with a biocompatible polytetrafluoroethylene barrier membrane (Ecoflon, St. Petersburg). A mucoperiosteal flap was applied to the site with the wound sutured carefully. The postoperative care included antiseptic treatment of the oral cavity, and application of antibacterial gel. The stitches were removed on Day 12. The time for the membranes to remain in the tissues — 2 to 8 weeks.

In case of jaws cystic lesions (G2), cystectomy was performed employing a standard procedure. In the experimental subgroup (ESG2), bone defects of small size (up to 20 mm in diameter) were filled with SVF-AT only. For plastic treatment of mid-sized bone defects (20–30 mm), SVF-AT was used with crushed bone added, which was taken from the patient through the surgery, from intraoral donor sites. To eliminate larger bone defects (exceeding 30 mm), including damage to one or both of the cortical jaw plates, granulated osteoconductor was introduced into the graft in addition to SVF-AT and bone chips (Bio-Oss, Switzerland). The resorbed collagen membrane (Bio-Gide, Switzerland) was placed under the mucoperiosteal flap prior to the wound closure. In the control subgroup (CSG2) with small and mid-sized bone defects, treatment was performed either under a blood clot or with an osteo-substituting material combined with a barrier membrane; for large sizes of cystic formations, cystotomy was the choice.

The study included modern methods of clinical, radiological, and instrumental diagnostics, as well

as cytological and morphological verification of the transplanted material and regenerated tissues. Control terms were set at 6, 12 and 24 months. To evaluate the treatment effectiveness, three categories of indicators were analyzed, including 1) the incidence of complications and positive outcomes; 2) the severity of the clinical symptoms; 3) the results obtained through instrumental, radiological and laboratory tests.

The study materials underwent statistical processing using the methods of parametric and non-parametric analysis based on the results of testing the compared sets for normal distribution. In the case of a confirmed normal distribution, the quantitative indicators were presented as arithmetic means (M) and standard errors (m). The quantitative indicators, whose distribution differed from the normal, were described through the values of the median (Me) and quartiles [Q1; Q3]. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The results of cytological tests indicate the reliability of the adipose tissue treatment protocol employed for obtaining SVF-AT. The cells were viable, demonstrated the immunophenotype of multipotent mesenchymal stromal cells (CD13+, CD34+, CD44+, CD90+, CD105+), actively reproduced in vitro and synthesized the extracellular matrix components. The number of viable nucleated cells in a SVF-AT used for a single surgery ranged from 25 to 120 million.

Using SVF-AT during DPTR improved significantly the clinical, functional and aesthetic results when treating patients with moderate to severe chronic periodontitis. The incidence of postoperative complications (infection and partial necrosis of the regenerate) was significantly lower in ESG1, compared with CSG1 — 2.1% and 19.1%, respectively ($p < 0.05$). After a cell-potentiated surgery, accelerated regression of inflammatory symptoms was observed with long-term stability of clinical indicators for the oral cavity status, such as gingivitis index, bleeding index, and periodontal index. The increase in the periodontal attachment after 2 years was 5.66 ± 0.02 mm in ESG1, which is 73% above the similar CSG1 indicator (3.27 ± 0.03 mm) where treatment was performed subject to the standard DPTR protocol ($p < 0.001$). Periotestometry indicated complete restoration of the periodontal support function in the ESG1 patients, while the majority of patients with CSG1 maintained pathological mobility. The average Periotest value 24 months after surgery was 3.8 ± 0.1 and 15.6 ± 0.3 points in the experimental and control subgroups, respectively ($p < 0.001$). An increase in the X-ray contrast structures prevailed in the area of

defects, the elimination of which was done with SVF-AT (Fig. 1).

The results of a comparative histomorphological study suggest significant inducing effect that SVF-AT has on the restoration of damaged tissues in the tooth supporting structures, which can be seen from the fact that the earlier biopsy material obtained from the ESG1 patients revealed the presence of marginal periodontal tissue soft structures featuring the specific short junction epithelium, new connective-tissue attachment, and the development of young alveoli bone structures. The average microvessels density on regenerating tissues sections in the experimental subgroup was almost 2 times as high as in the control one: 58.2 ± 10.2 and 30.1 ± 7.5 units per 1 mm^2 , respectively ($p = 0.047$).

Using SVF-AT in osteoplasty of maxillary defects after the removal of odontogenic cystic formations allowed a significant reduction in postoperative complications rate (1.7% versus 23.9%, $p < 0.001$), an increase in the frequency of positive clinical outcomes with no recurrence of inflammatory & destructive process in long-term observations (96.6% versus 47.8%, $p < 0.001$), achieving earlier and complete stabilization of mobile teeth as compared with conventional treatment methods. The results of X-ray study methods differed significantly in the studied subgroups, the method using SVF-AT autotransplantation appearing as more promising. In ESG2, after 2 months already, spot X-ray images showed uniform filling of jaws large defects with dense structures featuring no light spots in the central area, which was often the case in CSG2. In the long-term follow-up, most cases had no original defects boundaries visible, with a uniform trabecular structure of the reconstructed bone visualized. Computed tomography helped observe a return to the normal jaws anatomy without alveolar arch permanent deformations, with cortex and spongy bone in the intercortical area (Fig. 2).

Note to be made that there were no radiological signs of resorption in the newly formed structures, any ankylosis or resorption of the teeth roots in the long term. In CSG2, judging by the radiological signs, complete restoration of the bone was to be observed in relation to the alveolar crest smaller defects. In defects exceeding 20 mm, the development of radiologically relevant bone structures was observed only along the periphery, while the initial borders of the defect often remained visible.

According to the histological examination results, in smaller defects (up to 10 mm), reparative osteogenesis was identical in the compared subgroups and ended with the development of a sound bone. The recovery of mid- and large-size bone defects depended

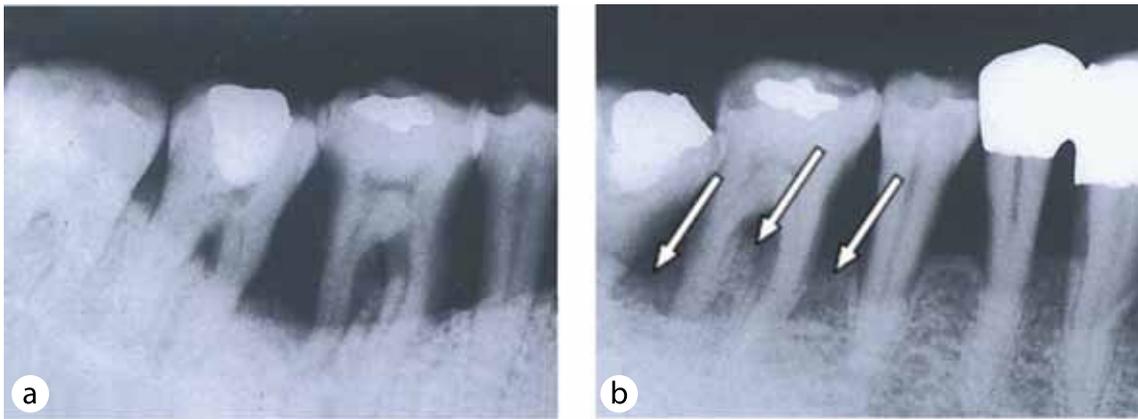


Fig. 1. Radiographic outcome of the replacement for furcation defect of the lower molar (FIII) and supraalveolar periodontal defects of the adjacent teeth: a) before treatment; b) after the DPTR with SVF-AT transplantation, a significant increase in the interdental space structures (shown by arrows)



Fig. 2. CT scan of the upper jaw, patient T. 16 years old: a) a large radicular cyst of the 1st jaw segment; b) 2 years after cystectomy and osteoplasty with transplantation of SVF-AT with bone chips into the bone defect: the defect is eliminated; the cortical plate restored; the jaw features normal X-ray anatomy

on the treatment offered. After transplantation of SVF-AT into the bone defect, the regenerate was soon after presented with reticulofibrous bone tissue, which filled the defect evenly regardless of its size; later on regenerate *maturation* to the lamellar bone of osteonic structure was observed (Fig. 3).

The recovery of larger bone defects in the absence of an additional source of regenerative cells and stimuli (such as SVF-AT) was incomplete. In the nearest term, the histological samples from CSG2 were observed to have a polymorphic regenerate of loose fibrous connective tissue with tough fibrous bone and chondroid tissue sites. In the longer term, the regenerate was delimited, the marginal area of the bone cavity featured

a mature bone, while the center was found to have moderately vascularized fibrous connective tissue.

DISCUSSION

Currently, the issue of safety is the cornerstone for cellular technology introduction. We did not observe any specific complications through the entire study, which indicates the absence of extra clinical risks in the implementation of SVF-AT autograft-potentiated treatment and rehabilitation methods for patients with inflammatory osteo-destructive dental issues. The technologies employed through this work are based on the use of newly isolated autologous minimally manipulated cellular material, which eliminates com-

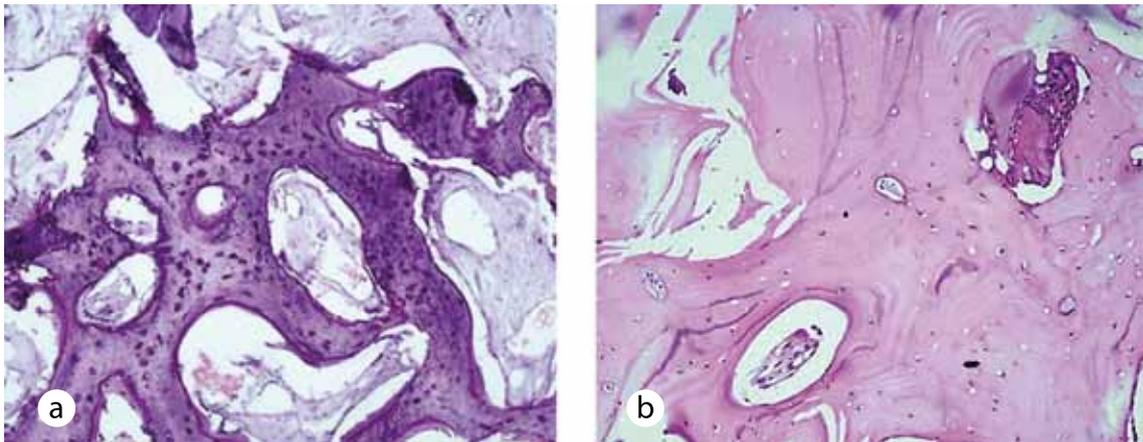


Fig. 3. Histomorphology of trepanbiopsy from the post-cystectomy jaw defect area at different periods after osteoplasty using SVF-AT: a) 4 months — primary trabeculae of reticulofibrous bone tissue; b) 18 months — mature mineralized bone osteonic structure. Stained with hematoxylin and eosin. Magn.: 480× (a), 280× (b)

pletely the disadvantages associated with the use of cell lines obtained *ex vivo*.

The results of the new treatments developed using SVF-AT exceed the results of the generally accepted approaches, evidence to that being the statistically significant differences in the total average values and relative indicators within the compared subgroups. It would be of interest to compare the registered (at the end of the 6-month follow-up period, common reference point) increase in periodontal (clinical) attachment (5.53 ± 0.02 mm) with the respective data available in literature. In their study, Y. Yamada et al. (2006) isolated mesenchymal stem cells from the bone marrow of the patients' iliac crest, then propagated them in a culture, combined with platelet-enriched plasma, and injected into periodontal defects. After 6 months, the increase in attachment was 4 mm [10]. R. Dhote et al. (2015) used a tissue-engineered construction of mesenchymal stem cells cultured on beta tricalcium phosphate combined with recombinant platelet growth factor. The patients were 14 people without systemic diseases, with an initial depth of periodontal pockets exceeding 5 mm. After 6 months, the increase in attachment was 3.91 ± 1.37 mm [11]. In case of periodontal regeneration with autologous bone marrow mononuclear cells on a gelatinous polymer carrier, Indian experts reached an attachment increase of 6 mm [12]. Our clinical results, in terms of the gained success, meet the results presented above by other researchers who have applied advanced cell transplantation and tissue engineering technologies, yet they feature certain advantage as they can be achieved in a safer, affordable and easily reproducible way.

The clinical outcomes demonstrate the safety and efficiency of the cell-potentiated approach in treating cystic issues in jaws. It is a known fact that when replacing long-existing defects with altered bone walls trophism, bioresorbable materials undergo organotypic rearrangement much slower, which requires special conditions that would improve blood supply to the defect area [13–18]. One of the reasons behind incomplete osteo-substitution of larger defects in the control subgroup was the lack of blood supply to the central parts of the graft due to remote location from the microcirculation stream along the defect periphery, as well as insufficient centripetal neovascularization rate. The regenerate histomorphology showed that under the same conditions, yet with SVF-AT, the osteoreparation outcomes changed radically. The reason for this, as we see it, was the *in situ* implementation of a number of positive SVF-AT properties, described in the literature for its cellular components and confirmed by the outcomes of their own experimental and cytological studies specifically for the fraction isolated according to a special protocol, i.e. 1) the capacity to stimulate osteogenesis, angiogenesis and neovascularization; 2) the capacity to provide mechanical stability in the wound due to the binding properties of the fibrous component, as well as to develop a functional matrix accessible for cellular interactions; 3) the capacity to differentiate and productively join the development of an organotypic regenerate [19–23].

CONCLUSION

Using the proposed cell-potentiated methods for the restoration of the jaws bone tissue allows a signifi-

cant increase in the efficiency of treatment offered to patients with osteodestructive dental diseases.

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