



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

## INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

<http://doi.org/10.5281/zenodo.1310584>

Available online at: <http://www.iajps.com>

Research Article

### PERSPECTIVES OF THE USE OF THE FACTORS GROWTH OF VASCULAR ENDOTHELY AND CYTOKINES, COLLAGEN MATRIX FOR STIMULATION OF REPARATIVE PROCESSES IN AUGMENTATION OF THE GUM

Tarasenko S.V<sup>1</sup>, Zagorskij S.V.<sup>2</sup>, Diachkova E.Yu.<sup>3</sup>

<sup>1</sup> M.D., PhD., professor, Chief of department of surgical dentistry of I.M.Sechenov First MSMU, Russia, Moscow, Mojaiskii val, h.11, 121059, e-mail.: [prof\\_Tarasenko@rambler.ru](mailto:prof_Tarasenko@rambler.ru)

<sup>2</sup> postgraduate student of department of surgical dentistry of I.M.Sechenov First MSMU, Russia, Moscow, Mojaiskii val, h.11, 121059, e-mail.: 5041579@list.ru

<sup>3</sup> PhD, assistant of professor of department of surgical dentistry of I.M.Sechenov First MSMU, Russia, Moscow, Mojaiskii val, h.11, 121059, email.: [secu2003@mail.ru](mailto:secu2003@mail.ru)  
phone number: +7-926-519-93-42

#### Abstract:

*In the analytical review the perspective methods of implantology and gingivoplasty are considered, which will allow to carry out the soft tissue of the gum in patients with diabetes mellitus, therefore, priding of such operations in these patients is considered problematic. The authors identified such methods as the use of collagen matrix in the soft tissue of the gum, saturated with vascular endothelial growth factor, and plasmolifting procedure based on the introduction of platelet-rich plasma taken from the patient's blood (contains growth factors). Diabetes is a disease in which the reparative processes of the soft tissues are decreased due to the low efficiency of angiogenesis. It is known that growth factors enhance the growth of new vessels, and this contributes to the reparative processes of soft tissues. In connection with it is noted the use of growth factors is promising in the development of soft tissues of the gum in patients with diabetes.*

*In the opinion of the authors, the selected methods will effectively stimulate the reparative processes in patients with diabetes mellitus, which will allow to successfully carry out operations for the growth of soft tissues in this category of patients. However, these theoretical conclusions made by the authors of the article are hypothetical and require verification in the framework of experimental and clinical studies.*

**Keywords:** *analytical review, angiogenesis, gum, implants, soft tissue, plasma, resorbable membrane, diabetes mellitus, platelets, vascular endothelium growth factor, nicotine.*

#### Corresponding Author:

**Diachkova E.Yu \***,

*PhD, assistant of professor of department of surgical dentistry of I.M.Sechenov First MSMU, Russia, Moscow, Mojaiskii val, h.11, 121059, email.: [secu2003@mail.ru](mailto:secu2003@mail.ru)  
phone number: +7-926-519-93-42*

QR code



*Please cite this article in press Diachkova E.Yu et al., Perspectives Of The Use Of The Factors Growth Of Vascular Endothely And Cytokines, Collagen Matrix For Stimulation Of Reparative Processes In Augmentation Of The Gum , Indo Am. J. P. Sci, 2018; 05(07).*

**INTRODUCTION:**

In addition to the aesthetic effect, the extension of the soft tissues of the gum allows to eliminate the effects of marginal periodontitis, as well as, in accordance with a number of modern scientific studies, it is necessary before the dental implantation. It should be noted that for a number of diseases periodontal disease is a consequence of the underlying disease, which increases the need for soft tissue build-up of the gum. These diseases include diabetes mellitus (DM). However, the presence of such pathology is a contraindication to implantological operations, in particular, operations for increasing of the soft tissue of the gums due to the worsening of reparative processes of soft tissues. To overcome this circulus vitosus, in our opinion is possible through the use of techniques that allow during these manipulations to stimulate reparative processes of soft tissues. The search for such methods based on the analysis of literature and determines the relevance of this article.

*1.The main methods of gum plasty.* Until recently, only two methods of mucosal augmentation have been used in the field of implantation: local tissue plasty or autotransplantation of a free flap from the donor site, most often from the hard palate. These methods are limited in use due to the complexity of the operation, high probability of postoperative complications.

Recently during the gingivoplasty surgeons begin to use a resorbable collagen matrix along with epithelial autotransplantation. It should be noted that a freely transplanted epithelial autograft does not receive supplement from the wound bed, so it does not grow, but is replaced by a newly formed mucosa. This is due to the fact that the internal reserves of the flap are not enough for a long regeneration process. Thus, after a certain time, the transplanted autograft turns into the same collagen matrix or membrane, which does not regenerate itself, but contributes to the normal regeneration and restoration of the wound surface. Therefore, the collagen membrane is similar to a free gingival autograft, which allows its use for augmentation of soft gum tissues with no less efficiency than autografts.

Collagen matrices can be successfully used in all cases when mucosal autograft transplantation is required. The results show that resorbable collagen matrices are advisable to use:

- to increase the volume of the attached mucosa in the area of the installed dental implants;
- to deepen the vestibule of the oral cavity;
- in case of closure of the deficit areas of the surgical field as an alternative to connective tissue graft [1].

The use of collagen matrix does not cause inflammatory reactions of surrounding tissues [2]. Materials based on collagen are widely used during osteoplasty and maxillofacial surgery due to their rapid biodegradation. Comparison of the results of the use of collagen matrix and connective tissue graft shows a lower prevalence of postoperative inflammation, an increase in the width of the area of the attached mucosa [3]. Thus, the use of collagen matrix can be considered as an adequate alternative to connective tissue graft.

*2.The role of vascularization in reparative processes in soft tissues.* The process of vascularization plays a great role in the engraftment of the resorbed collagen matrix. Vascularization is the process of formation of new vessels through the growth and branching of old vessels above and below the place of blood blockade in a larger vessel. Redundancy or insufficiency of vascularization leads to pathological processes. Insufficient vascularization is one of the known disadvantages of porous matrices for tissue engineering. This leads to insufficient delivery of oxygen, nutrients and cells, which is exacerbated by a decrease in soft tissue repair in a number of diseases. In the adult human body, angiogenesis is under strict control and is regulated by a number of stimulants and inhibitors. The stimulators of angiogenesis include growth factors. There are more than 10 factors that supply the growth of new blood vessels. Almost all of them are short peptides, 3 of them are better studied than others: vascular endothelial growth factor, fibroblast growth factor and angiogenin. Each of them was isolated from tissues with inadequately low blood supply. All angiogenic factors cause the growth of new vessels in the same way: they contribute to the appearance of new vessels by the growth and branching of old vessels [4].

*3.Reduction of angiogenesis during diabetes, as a problem of operations on the plasty of gum.* Diabetes, which is characterized by hyperglycemia and various metabolic disorders, leads to violation of the balance of angiogenesis. They disrupt the balance between proangiogenic and antiangiogenic regulators and lead to inadequate formation of new blood vessels in diabetes mellitus. In turn, disorders of angiogenesis are important mechanisms in the development of vascular complications of diabetes. So the development of macrovascular complications is accompanied with the suppression of the intensity of angiogenesis [5].

It is known that with poorly controlled diabetes mellitus the healing process of soft tissues slows down. At the same time, one of the factors is a decrease in the level of local growth factors, which limits the possibility of soft tissue buildup in the gum

during implantological operations [6]. It is also proved that in patients with DM the amount of collagen produced by fibroblasts decreases, which leads to a slowdown in wound reduction. Violation of carbohydrate metabolism entails an increase in matrix metalloproteinases (MMP) and a decrease in nitric oxide (NO), a transforming growth factor beta-1 (Tgf- $\beta_1$ ), which is the reason for slowing the formation of extracellular matrix. Clinical studies show that in diabetes mellitus a violation of the balance of angiogenesis can be achieved by using both angiogenesis inhibitors and its inhibitors stimulants. Stimulation of angiogenesis using stem cells and growth factors is a promising direction of treatment of insufficiency of angiogenesis during diabetes, which affect the healing process of soft tissues, formation of macroangiopathy.

*4. Stimulation of angiogenesis using a collagen membrane saturated with growth factor of vascular endothelium.* Considering the above-mentioned during increasing of the soft tissues of patients with diabetes seems to be promising to stimulate the process of angiogenesis through cytokines and growth factor of vascular endothelium. It seems hopeful to use collagen matrices for growth of gum tissue with the saturation of their growth factor of the endothelium of the vessels or to inject into the area of the collagen matrix blood plasma saturated with platelets. It is known that vascular endothelial growth factor and cytokines stimulate angiogenesis, and thus increase tissue oxygen saturation (SaO<sub>2</sub>) [7], which is one of the factors of soft tissue repair. The decrease in the level of this growth factor leads to a slowdown in the process of epithelialization [8]. Research results show that growth factors and cytokines have a decisive influence on the speed and quality of reparative processes in patients with diabetes [9].

The technology of saturation of resorbed collagen membranes with vascular endothelial growth factor is currently developed and tested. Membrane "Osteoplast" saturated with growth factor of vascular endothelium, developed by company "Proteinsintez" (Moscow). It is based on non-demineralized bone collagen in the form of blocks of 5x5x5 mm (LLC "NPK VITAFORM", Moscow), which was saturated with the growth factor of vascular endothelium [6].

Vascular endothelial growth factor is synthesized by recombinant protein production technology. The procedure involves obtaining the genetic constructs based on plasmid DNA containing DNA of the VEGF-A165 person. The plasmid vector is constructed on the basis of the modified pBK-CMV vector for expression in eukaryotic cells. As a producer cells of the line of SSS (ovaries of the Chinese hamster) are used. The CNO protein

produced by the cells of the FRES is purified from the culture medium by affine chromatography. The purity of the obtained protein was analyzed by electrophoresis in acrylamide gel, and the biological activity was analyzed using the analysis of proliferation of human umbilical vein endothelial dependent cells of human HUVEC.

Conjugation (cross-linking, croslinking) of the FRES with bone non-demineralized collagen is carried out using three different techniques. Cross-linking methods are chosen taking into account their chemical activity, compatibility with the material used, the size of the bridges formed between proteins, solubility in water and physiological fluids of the body of the final products of conjugation, preservation of the target biological properties of the material, in particular the ability to effectively induce the growth of new blood vessels [10].

Currently, studies are being conducted on the use of resorbed membranes from non-demineralized bone collagen saturated with vascular endothelial growth factor. Experimental studies in animals have shown that the use of a membrane saturated with vascular endothelial growth factor, the use of vascular epithelial growth factor to saturate the insulating membrane leads to a decrease in the processes of hypoxia in the area of surgical trauma, which is accompanied by the harmonization of angiogenesis, and leads to a complete resorption of the implanted bone fragment and the formation of a newly formed mature and fully formed bone tissue.

*5. Stimulation of angiogenesis with using the collagen membrane for increasing of the soft tissues of the gums, through the introduction of blood plasma enriched with platelets.* Japanese researchers [11] have also suggested using growth factors to increase the volume of gums. As a result of experiments, in which the injection of soft tissue immunodeficiency rat solutions containing human mesenchymal stromal cells, fibroblast cultures, suspension of hyaluronic acid and platelet-rich plasma growth factors, revealed significant differences in tissue growth in different combinations of cells. The most significant increase was observed when the cell suspension contained platelet-rich plasma. Therefore, the use of collagen matrices for enhancing the soft gum tissue to stimulate angiogenesis, it is possible to use the plasma rich in platelets. Currently developed and tested procedure plasmolifting based on the introduction of platelet-rich plasma taken from the patient's blood. This plasma contains growth factors and is a stimulant of angiogenesis. The procedure, in our opinion, is also effective in the development of soft tissues of the gum.

**CONCLUSION:**

Thus, the analysis of theoretical studies shows the prospects of application in the development of soft tissues of the gum in patients with diabetes collagen matrices saturated with vascular endothelial growth factor, or the introduction of plasma saturated with platelets into the gingival region. Both procedures enhance the process of angiogenesis, which will increase the degree of reparation of the fabric. The introduction of platelet-rich plasma into the gingival region is possible, both when using the technique of free gingival autograft transplantation and when using the collagen matrix, however, the most effective, in our opinion, is the use of a collagen matrix saturated with the growth factor of endothelial vessels. This procedure is simpler and less traumatic. Taking into account the actively ongoing development of methods of saturation of collagen matrices with the growth factor of the endothelium of vessels, in the long term, this procedure is the most effective, however, this theoretical conclusion is hypothetical, and requires verification in the framework of experimental and clinical studies. After the success of their results, it will be possible to talk about the possibility of using collagen matrices saturated with the growth factor of the endothelium of vessels for the soft tissue of the gums.

**List of Abbreviations**

DB – diabetes mellitus

DNA – deoxyribonucleic acid

MMP - metalloproteinases

NO – nitric oxide

SaO<sub>2</sub> – saturation of oxygen

Tgf-β1 - transforming growth factor beta-1

**REFERENCES:**

1. Baulin I.M., Badalyan V.A., Ryahovskii A.N. Experimental research of collagen matrix for gum volume increasing with the use of 3D-modeling. *Stomatologiya*. 2015; 94(5):8-10 [in Rus.] doi: 10.17116/stomat20159458-10
2. Tissue vascularization. Formation and growth of new blood vessels. *Human physiology* [ONLINE] Available at: <http://meduniver.com/Medical/Physiology/602.html> [Access 07<sup>th</sup> of July 2018]
3. Zaytseva E.L., Tokmakova A.Yu Effects of growth factors and cytokins on soft tissue regeneration in patients with diabetes mellitus. *Diabetes mellitus*. 2014; 1: 57-62 [In Rus.] DOI: 10.14341/DM2014157-62
4. Konenkov V.I., Klimontov V.V. Angiogenesis and vasculogenesis during diabetes mellitus: new concepts of pathogenesis and treatment of vascular complications. *Diabetes mellitus*. 2012; 4: 17-27 [In Rus.]
5. Muraev A.A. Observation of biological features of new osteoplastic material on the basis of non-demineralized collagen, containing factor of growth of vascular endothelium during bone defect filling. *Recent technologies in medicine*. 2012; 1: 21-26 [In Rus.]
6. Gubova V.M., Ivanov S.Yu., Muraev A.A., Zaytsev A.B., Yamurkova I.F., Migura S.A., Yantsen I.E. Experimental research of barrier function of collagen membrane Osteoplast during healing of bone defects. *Recent technologies in medicine*. 2011; 3: 35-38 [In Rus.]
7. Arnold F, West DC. Angiogenesis in wound healing. *Pharmacology & Therapeutics*. 1991;52(3):407-422. DOI: [http://dx.doi.org/http://dx.doi.org/10.1016/0163-7258\(91\)90034-J](http://dx.doi.org/http://dx.doi.org/10.1016/0163-7258(91)90034-J)
8. Nevins M., Nevins M.L., Camelo M., Camelo J.M., Schupbach P., Kim D.M. The clinical efficacy of dynamatrix extracellular membrane in augmenting keratinized tissue. *Int. J. Periodontics. Restorative. Dent*. 2010; 30: 151-161.
9. Boulton A.J.M., Cavanagh PR., Raymann g. 2006. New and alternative treatments for diabetic foot ulcers: hormones and growth factors. In: *The foot in diabetes*, 4th edition. John Willey& sons, Ltd. 214-221.
10. Werner S, Grose R. Regulation of Wound Healing by Growth Factors and Cytokines. *Physiological Reviews*. 2003; 83(3): 835-870.
11. Okabe K., Yamada Y., Ito K., Kohgo T., Yoshimi R., Ueda M. Injectable softtissue augmentation by tissue engineering and regenerative medicine with human mesenchymal stromal cells, platelet-rich plasma and hyaluronic acid scaffolds. *Cytotherapy*. 2009; 11 (3): 307-316.