REGENERATIVE THERAPY IN ORTHODONTICS

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ABSTRACT

Regenerative dentistry, as a subdivision of regenerative medicine, is a new field of research uses tissues' self-healing and regenerative potentials. The use of bone and bone substitutes, membranes, growth factors, stem cells, platelet concentrates and a combination of the mentioned cells and tissues, enables more successful dental treatment.

The aim of this review is to inform the wider orthodontic public about the possibilities of regenerative therapy in orthodontics.

Methods and materials: the research was done using search engines PubMed and Google Scholar. The keywords were: regenerative therapy, stem cells, orthodontics, PRF. Selected articles are written in the period of 2004-2018.

Conclusion: combined orthodontic and regenerative therapy can resolve complex clinical problems and enhance bone formation.

New technologies in dentistry, as well as more demanding orthodontic patients, have brought the application of regenerative methods in orthodontics. This article is a short review of the use of regenerative methods, mostly in the form of PRF and stem cells, in orthodontic treatment.

Keywords: regenerative therapy, stem cells, orthodontics, PRF

Introduction

The terms regenerative medicine, reparative medicine or tissue engineering are equally used in describing the use of cells, proteins, cell padding, signal molecules in reparation and regeneration of tissue [1]. The application of regenerative methods in treatment is a challenge for contemporary dentistry. These methods offer regeneration of certain tissues, self-regeneration and self-treatment, during which the body uses own products to regenerate.

The concept of tissue regeneration is taken from regenerative processes which occur in vivo. Regeneration of tissue, although a complex process, can be divided into three steps: inflammation, proliferation and remodeling [1]. During this process signal molecules increase the number of cells of damaged area, while morphogenetic signals induce differentiation of tissue. These signal molecules are mostly polypeptide factors of growth being produced by local cells or are delivered from circular blood and extracellular matrix. During that time the extracellular matrix has a role of padding for the migration of cells and their arrangement in the form of desired tissue. In *in vitro* conditions, there is a presence of triad including non-differentiated cells, signal molecules and instead of extracellular matrix, natural or synthetic tridimensional padding is used. Angiogenesis and vascularity take an important role in reparation of tissue considering that blood supply is necessary for the survival and cell development. It is also a source of undifferentiated perivascular cells which are required for the process of reparation [2].

Due to success in the field of regenerative medicine, it is possible to choose different treatments. Usage of bones and bone equivalent materials, membrane, growth factors, stem cells, platelet-rich fibrin (PRF) and a combination of the above mentioned, provides a possibility of rescuing and maintaining teeth, which would be extracted, ten years ago, due to a volume of loss of supporting structures. Regenerative medicine is new branch in the science started in the 21st century producing the development of regenerative dentistry.

Development of technology in dentistry contributed to bigger expectations in treatment results. New technologies in dentistry and more significant demands of patients lead to the fact that regenerative techniques are more and more used in orthodontics.

Orthodontic treatment, in general, especially at adult and children patients with cleft lip and palate demand interdisciplinary approach, so the application of regenerative methods in other disciplines (oral surgery, maxi facial surgery, implantology, periodontology, and endodontics) improves the orthodontist's performance.

The most commonly used regenerative products are stem cells and various blood products of which the PRF mostly.

Methods and Materials

Articles published in two databases (PubMed and Google Scholar) are searched and analyzed. Different keywords are used during the search: regenerative therapy, stem cells, orthodontics and PRF.

Inclusive criteria were: access to the paper in whole, articles published in English and papers published in the period from 2004 to 2018. Also, papers need to include one of the keywords in their title.

Results

High number of papers were found by searching, but only 20 of them satisfied the criterion. Eight of them were analyzed finally.

Discussion

Application of Stem Cells in Orthodontics

Stem cells are particular type of cells which can regenerate themselves and differentiate to other kinds of a cell [3].

In 2006 Yamanin discovered the way of "reprogramming in stadium similar to embryonic stem cells" in the adult mouse. The success of this method is related to the ability to manifest factors of pluripotent adult stem cells which reprogrammed them and returned to the stage of pluripotent stem cells.

Stem cells are part of multicellular organisms, and they are featured by regeneration by mitotic division of cells while they are in non-differentiate stage [4].

Stem cells are classified concerning their function (normal and cancer stem cells) or by the source of isolation (embryonic, fetal, stem cells from the blood of umbilicus and adult non-stem cells). The existence of human stem cells is proved to be in bone marrow, peripheral blood, hair follicles, epithelium of digestive system, skeletal and heart muscle, lungs, brain, liver, pancreas, fat tissue, synovium, periosteum, and teeth. Although they are in a relative state of sleep mode, these cells can react strongly to non-tissue damage [5].

Stem cells of the tooth can be isolated from:

1. epithelium
2. pulp
3. periodontal ligament
4. applied papillon [5]

In dentistry, the application of stem cells includes regeneration of dentine, support structures of tooth and reconstruction of craniofacial structures.

Application of stem cells in orthodontics is still experimental, and it is far from everyday usage.

Results obtained in this study are promising, in terms that stem cells and regenerative therapy will ease an orthodontist's work generally.

Stem cells in orthodontic therapy are mainly related to the regeneration of periodontium which is responsible for all procedures participating in teeth movement. Therefore, dental cement, periodontal ligament and alveolar bone are tissues in which specific changes occur, during the orthodontic therapy, under the influence of allied force causes teeth movement. There are several papers in which this revolutionary therapy method in experimental conditions is applied. A common application of orthodontics in adult patients demands the help of regenerative methods to ease teeth movement through sclerotic bone.

Xiaoyan Chen et all conducted research in which they applied mesenchyme stem cells to improve osteogenesis in orthodontic teeth movement. They started with the fact forces in orthodontics cause bone resorption on one side and apposition bone on the other side.

The results of the study confirmed that isolated mesenchyme steam cells (hJBMMSCs) taken from healthy donors ageing between18-35 are applied on the bone by *in vitro* conditions, stimulate the development of osteoblast and osteogenesis respectively and therefore, they make orthodontic therapy easier [6].

The other field of orthodontics tending to be improved by regenerative medicine is the splitting of an inter-maxillary suture with an expanding palate. Turkish scientists led by Abdullah Ekizerom conducted an experimental study. They did an experiment in which 19 rats were divided into two groups. In the control group they expanded a palate by splitting intra-pre-maxillary suture and in the tested group, they added mesenchyme stem cells when splitting the suture. Immune-histochemical analysis was conducted after the treatment applied on the samples.

Microscopic analysis showed a presence of excessive formation of the new bone, an increased number of osteoblast and more significant blood supply of intra-premaxillary suture of rats in the test group where mesenchyme stem cells are applied [8].

The problem which appears during teeth movement is a root resorption of the moved tooth. Application of stem cells is a way of preventing these complications.

This study is conducted on rats and it aims to explore and compare results of stem cells and gens of osteoprotegerin (OPG) applied to prevent or inhibit, under the influence of orthodontic forces, resorption of root already appeared.

An orthodontic force of 100 g on the upper first molar of rats and rats test group was injected with mesenchyme stem cells. Control orthopantomography was conducted on the first, sixth and eleventh day out of the total 14 days during which force application lasted.

The conclusion of the paper after application of described methods of regenerative therapy is that the number of osteoclasts, resorption lacunas and area of resorption of the bone is significantly smaller in the test group than in the control group [9].

Regenerative medicine is used in the study which researched orthodontic treatment of patients who had bone defects. Attia MS, Shoreibah EA, Ibrahim SA, Nassar HA in their paper "Regenerative therapy of osseous defects combined with orthodontic tooth movement" applied regenerative therapy on 15 patients, with at least three inter-bone defects and malocclusion. After they tested control group and

two ways of treatment: only orthodontic and combined regenerative-orthodontic therapy were successful.

Results showed that measured parameters (bone thickness, attached gingiva, bone density) were statistically and significantly improved in the test than in the control group [7].

Stem cells offer the potential of regeneration of defect of craniofacial bones, but this hasn't been clinically tested yet. This opens a possibility of using regenerative therapy in treating cleft lip and palate. A regenerative technique, used for reconstruction of cleft palate and lip included appliance of cell therapy and appliance of growth factor. Lack of proof, in controlled clinical studies, efficiency of treatment by compensating tissue in defect of cleft lip and palate cannot be defined [18].

The PRF in Orthodontics

PRF-platelet rich fibrin, which was first described by French scientist **Choukroun in 2000** presents the second generation of platelet concentrate which is gained by centrifuging the blood of patient with no anticoagulant and other biochemical modifications. PRF has a dense fibrin network with leukocytes, cytokines, structural glycoproteins and growth factors [10].

Due to its complex architecture and composition, biomaterial is presented with its unique mechanic features differentiating from other plates concentrates, such as PRP (platel rich plasma). Many studies show that healing with the help of PRF is faster with higher quality. [11,12]. PRF is considered to be more superior in relation to other platel concentrates, such as PRP, due to its simplicity and economic justifed (with no use of beef thrombin and other chemical modifiers), and also in relation to other surgical techniques (in which autotransplants are used) since it avoids the secondary operational field (donor area). Due to its advantages, PRF is a regenerative material which has taken a leading role in periodontology, oral surgery, implantology. Recently, it is used in combination with orthodontic treatment [13]. Each orthodontic intervention has periodontal dimension: orthodontic biomechanics and therapy plan are determined by periodontal factors such as length and shape of a tooth root, length and width of alveolar bone and gingiva structure [14]. Therefore, almost everyday application of PRF in periodontology has an important influence on orthodontics therapy, especially at adult patients.

Apart from PRF in periodontal surgery and therefore in orthodontics, collagen membrane can be used. They can be resorbing and non-resorbing. In practice, the former is used more. It is not necessary to pull out resorbing membranes after they are put in, which eases discomfort, eliminates unnecessary surgical complications and lowers costs for patients. Due to membrane features, their decomposition cannot be thoroughly monitored. Decomposing starts immediately after it is placed in tissue. The speed of decomposing can vary, especially if the membranes used are decomposing by enzymes such as collagen. Desirable period of membrane persistence in vivo ranges from 4 weeks to several months [19]. Resorbing membranes are divided into biological and synthetic.

Apart from collagen membranes, factors of growth and cell mediators regulating cell activities such as proliferation and migration, can be used. They perform locally and in low concentration. They are connected to membrane receptors of high affinity and they activate cell mechanisms in that way. Bone morphogenetic proteins are a group of proteins belonging to a group of transforming factors of growth. Mentioned factors can stimulate bones, cartilage, and cementogenesis as well. It is considered that they stimulate cells not only in the remaining periodontal ligament but also in the rest tissues, lobes for example [20].

Contemporary lifestyle demands faster orthodontic treatment; therefore a time of orthodontic therapy should be shortened. Since the main obstacle in faster teeth movement is cortical bone, the way of overcoming this obstacle is by surgical-orthodontic treatment and cortectomy, respectively.

Brothers Wilcko (periodontist and orthodontist) presented (in 2001) new technique surgically supported tooth movement. Their method combines classical cortectomy/osteotomy of alveolar bone with usage of bone transplant to maintain or increase the thickness of cortical plaque, in which teeth movement occurs.

Their method is called “Periodontally Accelerated Osteogenic Orthodontic or PAOO." Advantages which

this method brought are numerous: fast teeth movement, a short period of therapy, less resorption of root increased booming, accelerated traction of impacted teeth, the robustness of periodontal tissue and post-orthodontic stability [17].

Francisco Munoz et all made an interesting study in which he applied Leukocyte-Platelet Rich Fibrin (L-PRF) (with the previously described method of orthodontic therapy (PAOO)), after which he monitored clinical effects on swelling and pain of the patients.

This study concluded that application of L-PRF with PAOO method of orthodontic teeth movement has multiple advantages. Those are: reduce of postoperative inflammation, pain, and risk of infection and no adverse influence on teeth movement. This is very significant since the usage of common analgesic and non-steroid anti-inflammatory medicines influence negatively teeth movement [17]. Therefore, L-PRF is used as an alternative for these drugs, which inhibit orthodontic teeth movement.

The peak of regenerative therapy application in dentistry is teeth transplant, either from a donor or from artificially produced tooth in biomedical conditions. The progress of medicine is present in dentistry as well.

Japanese scientists demonstrated successful transplantation of biomedical raised tooth in a region of missing lower molar in *vivo* conditions in 4 weeks old mice. The tooth was implanted together with periodontal ligament and alveolar bone and was put into function [18].

This is the first study presented evidence of regeneration of the whole organ through transplantation of biomedical produced tooth. In this comprehensive study conducted by Masamitsu Oshima et all(2011.god) orthodontic force on transplanted tooth was applied, testing its periodontal ligament and their response is mechanic stress. Results of this study showed that applied force caused bone remodeling and concentration of osteoclast and osteoblast and during experimental teeth movement is increased also. Authors, in this way, proved the function of periodontal ligament of a new transplanted tooth [18].

Conclusion

We can conclude that regenerative therapy in orthodontics has the following performances**:** stimulates creation of osteoblast and osteogenesis thus easing the orthodontic treatment, increasing production of new bone, increasing number of osteoblasts and the blood supply of inter-premaxillary suture in widening palate, decreasing root resorption of moved tooth, shortening the time of adverse effects of orthodontic therapy and giving the possibility of transplant of biomedically produced tooth and adequate response to applied force of transplanted tooth.

Significant progress in this area, however, opens ethical issues, considering numerous experiments, which in the hands of immoral scientists, can be extreme.

Combination of orthodontic and regenerative therapy can solve complex clinical problems and significantly improve bone formatting.

References

1. Melek L. Tissue engineering in oral and maxillo-facial reconstruction. Tanta Dental Journal. 2015;12(3):211-223.
2. Lanza R, Langer R, Vacanti J. Principles of tissue engineering. Amsterdam: Elsevier Academic Press; 2007.
3. P.E. Chandra Mouli, S. Manoj Kumar, B.Sentil et al. J. Pharm. Sci. & Res.2012 Vol.4(7), 1872 - 1876
4. Fortier LA. Stem cells, classification, controversies and clinical aplicatoion. Vet Surg. 2005 Sep-Oct;34(5):415-23.
5. Todorović V., Marković D., Milošević-Jovčić N., Petakov M., Balin B., Čolić M., et al. "Dental pulp stem cells - potential significance in regenerative medicine", Serbian Dental J 2008. vol. 55, br. 3, str. 170-179
6. Chen X., Liu Y., Ding W., Shi J., Li S., Liu Y., et al."Mechanical stretch-induced osteogenic differentiation of human jaw bone marrow mesenchymal stem cells (hJBMMSCs) via inhibition of the NF-κB pathway" C Cell Death and Disease 2018; volume 9, Article number: 207

7. Attia M.S., Shoreibah E.A., Ibrahim S.A., Nassar H.A., "Regenerative therapy of osseous defects combined with orthodontic tooth movement" Journal of the International Academy of Periodontology 2012 14/1: 17-25

8. Ekizer A.; Yalvac M. E., Uysal T., Mehmet Fatih Sonmez M. F., Sahin F., "Bone marrow mesenchymal stem cells enhance bone formation in orthodontically expanded maxillae in rats" The EH Angle Education and Research Foundation 2015. Vol. 85, No. 6, pp. 1084-1085.

9. Nisa Gul et al. "Effects of cell-mediated osteoprotegerin gene transfer and mesenchymal stem cell applications on orthodontically induced root resorption of rat teeth"European Journal of Orthodontics, Volume 39, Issue 3, 1 June 2017, Pages 235–242 June 2017.

10. Dohan D.M., Choukroun J., Diss A., Dohan S.L., Dohan A.J, Mouhyi J., et al.Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg 8. Oral Med Oral Pathol Oral Radiol Endod. 2006 Mar;101(3):e37-44.

11. Sharma A., Pradeep A.R. Treatment of 3 wall intrabony defects in patients with chronic periodontitis with autologous platelet rich fibrin: a randomized controlled clinical trial. J Periodontol 2011; 82(12):1705-12

12. Thorat M., Pradeep A.R., Pallavi B. Clinical effects of autologous platelet rich fibrin in the treatment of intra bony defects: a controlled clinical trial. J Clin Periodontal 2011; 38(10):925-32.

13. Ristić T. DOCTORAL DISSERTATION "Evaluation of platelet- rich fibrin efficiency in gingival recession treatment" 2016.

14. DiedrichP., Fritz U., Kinzinger G. Interrelationship between Periodontics and Adult Orthodontics. Perio 2004 : Vol 1, Issue 3 :143-149

15. Kaigler D., Pagni G., Park, C.H., Braun T.M., Holman L.A., Yi E. et al. Stem Cell Therapy for Craniofacial Bone Regeneration: A Randomized, Controlled Feasibility Trial.Cell Transplant. 2013; 22(5): 767–777.

16. Khojasteh A., Kheiri L., Motamedian S.R., Nadjmi N.Regenerative medicine in the treatment of alveolar cleft defect: A Systematic review of the literature.J Craniomaxillofac Surg. 2015 Oct;43(8):1608-13.

17. Munoz F., Jiménez C., Espinoza D., Vervelle A., Beugnet J., Haidar Z.Use of leukocyte and platelet-rich fibrin (L-PRF) in periodontally accelerated osteogenic orthodontics (PAOO): Clinical effects on edema and pain. J Clin Exp Dent. 2016 Apr; 8(2): e119–e124.

18. Oshima M., Mizuno M., Imamura A., Ogawa M., Yasukawa M., Yamazaki H. et al. Functional tooth regeneration using a bioengineered tooth unit as a mature organ replacement regenerative therapy.PLoS One. 2011;6(7):e21531.

19. Reichert C., Klein M., Kasaj A., Kuhn S., Gotz H., Hommel G.et al. Modulacija morfologije osteogenih stanica pomoću ECM liganada i derivata caklinskog matriksa. Acta Stomatol Croat 2009; 43 (3): 188-201.

20. Clerenhugh V, Tugnait A, Genco J. R. Periodontology at a Glance. Wiley-Blackwell 2009; 52- 53.