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TISSUE–ENGINEERED BONE IMPLANTS FOR THE REPLACEMENT OF JAWBONE DEFECTS. LITERATURE REVIEW

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SUMMARY

The purpose of the study: *to trace the development of methods of bone implants for the replacement of jawbone defects: from ceramic and polymeric scaffolds to complex tissue-engineered structures with stem cells, growth factors and vascular anastomoses based on literature data.*

Materials and methods: *searching, systematization and analysis of scientific data on various types of 3D-printed bone implants and their effectiveness in replacing bone defects.*

Conclusions: *Modern technologies of 3D-printing, cell and tissue engineering, microvascular surgical techniques closely approach scientists and clinicians to creation of an artificial bone implant which in the body must become a living structure capable of integrating with the patient's bone. Only complex approach which includes reconstruction of the implant of individual shape and sufficient mechanical strength, giving of osteoinductive and osteogenic properties, providing of internal axial and external angiogenesis is the basis for such tissue-engineered construction.*

KEYWORDS: *artificial tissue implants, bone vascularisation, bone implants, bone engineering, bone the defects reconstruction, arteriovenous loop.*

CONFLICT of INTEREST. *The authors declare no conflict of interest.*

Introduction

Tissue damage caused by trauma, cancer and infectious processes can lead to extensive defects and deformities requiring reconstructive surgery. More than 500,000 people with head and neck cancers are identified each year (Cohen et al., 2018). Modern surgical treatment of malignant lesions implies one-stage removal of resection defects. For this purpose, vascularized bone or combined bone-soft tissue autografts are the «gold standard» [Huang et al. [Huang et al., 2016]. For example, for mandibular reconstruction, the peroneal autograft on microvascular anastomosis is most often used. Its advantages are a long vascular stem, vessel diameter, suitable length and thickness of the bone, the possibility of performing reconstruction over a long distance, the possibility of including a muscle or skin component with a flap, stable bone structure that allows intraosseous implantation and further orthopedic prosthesis, minimal resorption [Tereshchuk et al., 2018].

However, all autotransplant surgeries have disadvantages and limitations. First, it is an additional surgical procedure of graft taking, defect or instability of the donor site, deformation and pain in the donor site, risk of infection (Lakhiani et al., 2016; Simon et al., 2003; Hartman et al., 2002). The main factor determining the nutrition and «survival» of the graft at the microvascular anastomosis is the patency of the anastomosis itself. This can be influenced by surgical technique, anaesthetic and medication support, and postoperative regimen.

Despite the impressive success of microsurgical procedures in tissue and organ transplantation, the development of artificial tissue-engineered constructs to replace bone and other tissue defects is a promising area. Advances in cell engineering (the ability to cultivate deterministic cells), genetics and molecular biology (synthesis of cytokines and growth factors), 3D-printing of matrices and scaffolds of the right shape with biocompatible materials facilitate this.

This review focuses on current advances in tissue engineering in the development of vascularised tissue implants (VTIs), especially bone implants. The requirements for VTIs are described and systematised, the technologies for VTI creation are reviewed and the results of their use *in in vivo* experiments are given.

Materials and methods

The scientific literature for this review was collected from the following on-line databases and libraries: https://elibrary. ru/, https://scholar. google. ru/, https://pubmed. ncbi. nlm. nih. gov, https://www. sciencedirect. com/. Search was performed using the following keywords: artificial tissue implants, bone vascularization, bone implants, bone engineering, bone defect reconstruction, arteriovenous loop; no date restrictions.

Discussion

3D-prototyping of bone implant

Currently, it is possible to produce a biocompatible bone implant (scaffold) of any geometric shape, including an individual one for each particular patient using 3D-printing [Tereshchuk S. V. et al., 2019, Kim et al., 2021].

Due to the nature of the material used for 3D-printing and the architectonics of 3D-printing, bone implants usually have osteoconductive properties, i. e. they are a matrix for bone tissue formation on their basis. Adding growth factors, cytokines and cells to their composition can additionally give osteoinductive and osteogenic properties [Muraev A. A. et al., 2013].

Thus the usage of biphasic calcium phosphate as a scaffold is much more effective than using pure hydroxyapatite and beta-tricalcium phosphate (HA and b-TCP) [Kohri M et al., 1993; Nery et al., 1992]. The pores and their number and size in the scaffold play an important role in the process of surrounding tissue ingrowth into the material and the osseointegration of the material. If the pore size is below 100 μm, fibrovascular encapsulation of the implant may occur; 100–500 μm is considered optimal [Kühne et al. 1994].

In addition to its effect on the regeneration of the bone tissue itself, pore size affects vascular growth, which is more pronounced in large pores (Druecke D et al., 2004).

It is important to understand that in order for a complete bone implant to form, a vascular structure must be formed in its structure to nourish it.

External and internal vascularisation

Vascularisation is a key link in the growth of new and regeneration of damaged tissue. When creating osteoplastic materials for the replacement of small bone defects, vascular endothelial growth factor (VEGF) may be included in the material composition. Thanks to VEGF a well-developed microcirculatory channel is formed in the regeneration zone [Muraev A. A. et al., 2012; 2012].

This approach refers to external neovascularisation, i. e., the microvascular bed is «connected» to existing adjacent

Results of the study

	https://elibrary.ru/	https://scholar. google. ru/	https://pubmed.ncbi.nlm.nih.gov	https://www.sciencedire ct. com/.
Artificial tissue implants	1	45	8198	15
Bone vascularisation	35	1850	97	1347
Bone implants	1248	32200	1034	14609
Bone engineering	256	11300	373	988
Bone defect reconstruction	42	2030	179	294
Arteriovenous loop	49	2520	210	520

arterioles. This type of neovascularization is ineffective when the size of the bone defect is large and in places that have been exposed to radiation [Lokmic Z et al, 2006; Tanaka et al, 2000]. This is the reason why the formation, development and survival of new cells in the centre of large constructions is limited at the beginning of vascularisation. If when a scaffold is implanted into an area where there is good vascularisation there will be development of a vascular network, then further transplantation into the recipient area will result in cessation of blood supply, as there is no subsequent connection to the vascular network in the defect site.

These problems have led to the development of new methods of neoangiogenesis for artificial tissue-engineered constructs, namely internal vascularisation. Internal vascularization is a method in which an artery or vein serves as a source of new vessels for tissue creation, which further allows the implant to be transferred to the recipient area by means of microvascular anastomoses [Tanaka Y et al., 2003; Erol et al., 1980; Khouri et al., 1991].

As mentioned above, 3D-printing allows the creation of artificial implants of defined macro- and micro-architecture. Therefore, the next step, in order to provide internal vascularisation, was to prefabricate channels for the vascular bed within the bone implant. With the prefabrication techniques it is possible to obtain the desired vascularised flap with an axial type from a flap with incidental vascularisation. With the arteriovenous loop it has become possible to implant grafts in highly vascularised areas and after a certain period to graft with connection to the local vascular network with microvascular anastomoses for tissue and cell feeding.

3D-printing of the channels for the new vessels should be guided by the structure of the vascular bed of the jawbone tissue and the surrounding vessels. The diameter of the lingual artery is 2.3±0.1 mm, the facial artery is 2.2±0.2 mm, the diameter of the maxillary artery is 3.3±0.3 cm [Lukyanov V. G. 1971] According to Jiang G. H. et al. the diameter of the left facial artery is 1.4–4.7 mm (mean 2.83±0.77 mm), the right one is 1.6–4.3 mm (mean 2.81±0.79 mm) [Jiang et al., 2008].

Volikov V. V. described the structure of the microvascular system of the maxilla alveolar process in norm and in case of tooth loss. Thus, in the presence of all teeth, the vascular system is represented by tubular structures with a rounded cross-section, located mostly perpendicular to the bone surface, with numerous anastomoses. The vascularisation of the bone tissue is satisfactory. The arterial vessels have a thin wall.

The diameter of the veins exceeds the diameter of the arteries by 2–4 times. Morphometric analysis of the periodontal vessels revealed that in intact dentition the number of vessels in 1 sq.mm. in the projection of the 11th tooth was 18,25 ± 3,58, in the projection of the 21st tooth – 19,05 ± 3,26, in the projection of the 16th tooth – 19,10 ± 4,01, in the projection of the 26th tooth – 19,30 ± 3,27 (at $p<0,05$). In the projection of all studied teeth the number of vessels in 1 sq.mm. was more in women in comparison with men. In comparison with the group of patients with intact dentition in partial and total adentia the number of vessels in 1 sq.mm. decreased by 20 % and 60 % respectively, vessel diameter was 40 % and 70 %, the thickness of the vascular wall increased by 2 and 4 times respectively. [Volikov V. V. et al., 2015].

Revascularised bone implants

The next step in the evolution of artificial bone implants (ABI) was to combine the tissue-engineered structure with living vessels by introducing a main feeding vessel into them. As such a vessel an arteriovenous loop or a vascular stalk is used, which is placed directly in the bone implant (BI) or under it. It was shown that the feeding vessel allows good vascularization of the BI, due to the formation of a microcirculatory channel around it [Khouri et al. 1991; Tan et al., 2004; Hirase et al., 1987; Morrison et al., 1990]. Such work is actively carried out *in vivo* on animal models. For this purpose the highly vascularized regions are chosen, where the prefabricated BI is placed and after some time it is transferred into the bone defect with the connection to the local vascular network with the help of the microvascular anastomoses. The vascular axis becomes a supporting vessel after transplantation and microsurgical anastomoses with the local vessels to allow the new vessels to live and integrate.

As an axial vessel, the arteriovenous loop has proven most effective (Tanaka et al., 2003; Cassell et al., 2002; Kneser et al., 2006).

Because of mechanical stimulation, the level of VEGF (vascular endothelial growth factor) increases when a vascular graft is introduced into the arterial circulation (Nath et al., 2003; Dvorak et al., 1995). The local inflammatory reaction that occurs during surgical intervention on a vessel causes an angiogenic reaction. VEGF levels in platelets increase under the influence of proinflammatory chemokines [Nath et al., 2003]. In microvascular anastomoses there is an increase in endothelial cells in microvascular anastomoses due to the combination of blood shear stress and turbulent current changes [Davies et al., 1986].

Once the main vessel in the BI is integrated and the vascularisation process is complete, the BI is transferred to the recipient area to repair the bone defect and connected to the recipient vessel. By 8 weeks, there is significant vascularisation of the matrix with an arteriovenous loop (Kneser et al., 2006).

Arteriovenous loop

An arteriovenous loop (AVP) is a pathological direct connection between an artery and a vein (congenital or acquired), creating blood flow bypassing the capillary network. Pathological to normal tissues, in the experiment AVP promoted flow-induced axial vascularisation. Thus, placed in the central part of the bone implant, AVP is a source of «axial vascularization», which in combination with peripheral angiogenesis («external vascularization») provides adequate blood supply and thus opens significant prospects in solving the problem of increasing the survival of cells comprising the BI [Leibig et al., 2016].

In 1980, Erol and Spira developed the arteriovenous loop method (AVP) in experimental animals [Erol et al., 1980;]. The authors used rats weighing 250–350 grams. An artery and vein were exposed on one side of the femoral vessels, and a venous graft was obtained on the other side. Next, the vessels were prepared by ligating the proximal part of the vein and the distal end of the artery. The venous graft was washed with heparin and then two end-to-end anastomoses were applied: the proximal end of the artery and the distal end of the vein. The criterion of the vessel patency was the pulsation of the venous loop. The loop was inserted into the implantation chamber and then closed from above with the second part of the implant. The chamber was closed and tied with 6/0 non-absorbable sutures. The skin was sutured 4/0–5/0. Postoperatively, heparin was injected intravenously. IVG (interpositional vein grafts) is necessary to avoid tension in the loop between the artery and vein, and is a good inducer for early angiogenesis (Polykandriotis et al., 2007; Schmidt et al., 2013). The loop is completely isolated, allowing vascularisation at the expense of the AV loop. This results in hypoxia in the chamber, which is a stimulus for neoangiogenesis. Hypoxia and cell proliferation reach their peak on day 7 [Lokmic Z et al, 2006].

Experiments using the arteriovenous loop method are also possible in other animals such as rabbits, dogs, sheep [Wu X et al., 2015; Eweida et al., 2017; Dong et al., 2012]. Experiments on larger animals have provided the rationale for the clinical use of the method.

AVP has been used in various experimental models. To create the BIs, the AVP method was combined with different scaffolds, including growth factors and cells: mesenchymal stem cells (MSCs) [Arkudas et al., 2017; Kim HY et al., 2018; Boos et al., 2012; Buehrer et al., 2014] or osteoblasts [Arkudas et al., 2007]. For cell differentiation, a number of authors have added specific growth factors to CIs. The combination of MSCs (mesenchymal stem cells) and BMP-2 (Bone morphogenetic protein-2) leads to accelerated bone development in the AB loop [Buehrer et al., 2014].

There are studies that focus on the possibility of growth of muscle tissue, heart tissue, soft tissue, lymphatic vessels and internal organs [Tee et al., 2012; Messina et al., 2005; Witt et al., 2017; Fiegel et al., 2008; Brown et al., 2006; Robering et al., 2018].

Work on lymphatic vessels is at a very early stage and clinically very much in demand, with Jan Robering working on lymphatic tissue development using an AV loop [Robering et al., 2018].

Bone implants can be different in sizes, depending on the zone of the defect, the size of the AVP is chosen according to its size (Cassell et al., 2001; Hofer et al., 2003). It has been shown that creation of additional external perforations in the BI results in faster vascular growth from the surrounding implant tissues [Dolderer et al., 2010]. Thus, in perforated implants there is an increase in angiogenesis in the arteriovenous loop due to the connection to the additional external vascular network, which significantly reduces the time of pre-vascularization and tissue formation [Arkudas et al., 2012].

Preclinical *in vivo* studies on large animals using a long AVP and large BIs of clinically relevant size can be considered. Justus Beier et al. in a study on sheep formed an AVP using a saphenous artery and femoral vein in a large model, with an implant size of 2.8 cm long, 1.8 cm wide and 1.8 cm high and with a volume of 16 cm [Beier et al., 2009]. Wu X in a study on dogs formed an AVP from the saphenous artery and femoral vein, which allowed the IVG not to be used [Wu X et al., 2015]. The success of this technique has also been shown in rabbits using the saphenous artery and femoral vein [Eweida et al., 2017].

Studies have shown that the less flexion of the AVP, the less likely to develop thrombosis, also the non-use of IVG (interpositional vein grafts) simultaneously with saphenous artery and femoral vein anastomosis is possible, as the anastomosis length between the artery and vein is sufficient and there is no tension [Dong et al, 2012; Weigand et al., 2015; Eweida et al., 2013]. However, several studies show that IVG (interpositional vein grafts) is an important factor in angiogenesis [Polykandriotis et al., 2007; Schmidt et al., 2013].

There may be a reduced risk of thrombosis with the AV-beam, less surgical experience is possible with this technique, but studies show that the loop is more effective for angiogenesis within the scaffold. The vascular bundle has a lower degree of vascularisation but better balance between the bone formation and the scaffold [Rudolph et al., 2020].

Conclusion

Modern 3D-printing, cell and tissue engineering and microvascular surgical techniques have brought scientists and clinicians closer to the creation of an artificial bone implant, which in the body must become a living structure capable of integrating with the patient's bone. Only a comprehensive approach that includes recreating an implant with an individual shape and sufficient mechanical strength, imparting osteoinductive and osteogenic properties, ensuring internal axial and external angiogenesis, is basic for such a tissue-engineered structure.

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