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Effect of Platelet-Rich Fibrin Combined with Guided Bone Regeneration on Bone Formation of Peri-Implant Bone Defects

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LY and XM conducted the experiments in this study. CW contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
PRF combined with GBR, Peri-implant bone defects, Osteogenic capacity, Immediate implant placement

ABSTRACT

Platelet-rich fibrin (PRF) combined with guided bone regeneration (GBR) is an emerging treatment method. The purpose of this study was to demonstrate the effects of PRF on the osteogenic ability of peri-implant bone defects. The sample of 67 patients who needed dental implants in Hebei Provincial Eye Hospital from March 2021 to March 2022 were randomly grouped: experimental group (immediate implant placement + implant covering PRF, n=40) and controls (immediate implant placement, n=27). The patients were followed up for 6 months to evaluate the treatment effect. The osteogenesis ability of the two groups at different time points and the state indicators around the implant before and after treatment were observed. At different time points after operation, the bone width and bone height in experimental group were higher as against controls (P<0.01). The level of bone resorption in experimental group was higher as against controls (P<0.05). There was no significant difference between two groups before treatment (P>0.05). The plaque index, sulcus bleeding index, probe bleeding index, and periodontal probe depth in experimental group were better as against controls (P<0.01). It was concluded that the use of PRF plus GBR in the treatment of patients with bone defects in periodontal disease can greatly reduce the adverse reactions of patients, effectively improve the periodontal status indicators, and shorten the recovery period of the disease.

INTRODUCTION

In recent years, an emerging oral implant technology, immediate implant placement technology, can restore the dentition to order immediately by removing the residual teeth and placing the implant into the fixed denture. Compared with traditional dentures, implant prostheses do not need base clings to fix the dentition, and this technology can restore the dentition with beautiful appearance, good comfort, excellent bite force, and obviously shorten the postoperative edentulous period of patients. This technology is efficient, economical, and more acceptable to patients (Busenlechner *et al*., 2016; Fürhauser *et al*., 2016). However, for other cases with difficulty in conventional restoration, such as tooth missing at free end, dentition defect with alveolar ridge atrophy, adequate bone mass support is required after immediate implant placement. If the bone height and bone mass of alveolar bone are seriously deficient, the operation of immediate implant placement will be difficult to carry out. Severe bone defect is an important factor leading to implant loss following oral implantation (Elgali *et al*., 2017; Wessing *et al*., 2018).

Implant is a common method to restore missing teeth and has become a hot research direction in the field of modern prosthodontics. However, a common problem in dental implant surgery is bone defect around implants, which seriously affects the stability and clinical effect of implants. Therefore, how to effectively promote the repair and regeneration of peri-implant bone defects and improve the osteogenic ability of bone defects has become a research hotspot in the field of dental implants. Typical treatment methods for periodontal bone defects include guided tissue regeneration, bone transplantation, and the application of enamel matrix derivatives (Li *et al*., 2018). With the development of science and technology, GBR

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has also been applied to stomatology, which is a common technique to solve bone defects after dental implantation. At present, bone substitutes that can be adopted in oral and maxillofacial fields include autogenous bone, allogeneic bone, xenogeneic bone, and artificial inorganic materials. Autogenous bone has better biocompatibility, bone conduction, and induction of bone regeneration than other bone materials. It is a good bone substitute material because of its rapid healing after implantation. However, autogenous bone has disadvantages such as limited amount of desirable bone, the need for additional surgical points, and easy infection of the bone harvesting site (Tettamanti *et al*., 2017; Fillingham and Jacobs, 2016). With the continuous renewal of artificial bone replacement materials, synthetic inorganic bone replacement materials have shown good biocompatibility, bone conduction, and bone regeneration induction, and are widely applied in the repair of tooth defects (Zhang and Zhang, 2018). Platelet-rich fibrin (PRF) plus bone regeneration (GBR) has become an emerging treatment. PRF is an autologous blood product that is prepared by rapid centrifugation and coagulation. PRF is rich in growth factors and cell adhesion molecules, which can promote cell proliferation and tissue regeneration (Dohan *et al*., 2018). In addition, PRF can also form a kind of biological scaffold in the defect area to promote the colonization and growth of osteocytes. Therefore, PRF plus GBR has been widely adopted in the treatment of peri-implant bone defects.

It is a new type of PRF preparation equipment, which can prepare PRF with more stable and rich growth factors (Pavlovic *et al*., 2021). However, there is no clear understanding of the role of PRF plus GBR in the treatment of peri-implant bone defects. Through the application of PRF complex, it can promote bone regeneration and repair, and improve the osteogenic ability of bone defects around implants. This technique is safe, reliable, effective, and simple to operate.

It is the purpose of our experimental intervention study to review the research progress and clinical application of PRF plus GBR, explore the combined effect on osteogenic ability of peri-implant bone defects, and prospect its future development, to provide reference for clinical practice.

MATERIALS AND METHODS

67 patients who needed dental implants and received treatment in the Department of Stomatology of Hebei Provincial Eye Hospital from March 2021 to March 2022 were enrolled. They were randomly divided into experimental group (immediate implant placement+implant covering PRF, 40 cases) and controls (immediate implant placement, 27 cases), with an average age of 45±15.

Inclusion criteria: if CT examination showed bone defect around implant, immediate implant treatment could be performed. There was no severe inflammation in the implant area, and the patient's oral hygiene was clean and excellent. Exclusion criteria: Patients with bone defects and gingival bleeding. Patients with malocclusion, molars, and unilateral chewing. Patients with basic metabolic diseases, autoimmune diseases. Patients with smoking habits and poor oral hygiene.

Preparation of PRF

A 10 mL sample of the patient's platelet-rich blood was drawn and placed into a test tube without anticoagulant, and the platelet suspension was subjected to three freeze-thaw cycles to release fibrin-rich particles. After centrifugation (1,200r/10min), the sample in the test tube was divided into three layers, the bottom layer was red blood cell debris, the top layer was clear liquid, and the middle pale-yellow gel sample was the required sample for this experiment. The middle layer was removed by using sterile tweezers, which was called PRF. The remaining liquid in the test tube was removed to obtain the original PRF gel, and then it was placed in a dry and sterilized incubator for 10 min to allow it to contract naturally. It was extruded and shaped to prepare PRF film with good elasticity and toughness.

During the preparation process, attention should be paid to the strict asepsis of the operation to ensure the purity and quality of the material. Parameters such as the number of freeze-thaw cycles, the time, and power of ultrasonic treatment needed to be optimized to obtain the best fibrin extraction.

Surgical method

Before the surgery, the patient's facial tomography was taken and recorded to observe the patient's adjacent teeth and bone mass in the implant area. The appropriate implant was selected according to the physiological and anatomical structure of the patient's mouth and teeth and their bone mass. After the preoperative examination, the patient's oral cavity was cleaned and the maxillofacial region was disinfected with compound chlorhexidine mouthwash. A surgical towel was spread around the patient's oral cavity, and the patient was treated with local oral anesthesia using Primacaine. The surgical operation area was entered through the oral incision, and the tissue layer was cut along the gingival sulcus until the position of the jaw bone surface. The masseter muscle was then blunt-separated below the periosteum, where care needed to be taken to protect the frontal nerve from injury. After the surgical field was fully exposed, the adhesion soft tissue and granulation tissue on the bone surface were

completely removed. The cancellous bone was cut from the anterior superior iliac crest and minced in advance, so that the diameter of the granular bone was 2-4 mm. The granular bone and PRF were mixed and implanted into the bone defect area, which was covered with medical guided tissue regeneration collagen repair membrane. Following proper fixation with fine silk thread, the oral mucosa was tightly sutured and bandaged under pressure. The stitches were removed after 1 week.

Controls used GBR only for immediate implantation. The experimental group was treated with PRF plus GBR for immediate implantation.

Postoperative anti-inflammatory

Both groups of patients needed to take oral cefixime capsules (H20040323, specification: 50 mg×8 tablets, 100 mg/time, twice a day) and oxacillin sodium capsules (H37022581, specification: 0.25 g×24 capsules, 0.15 g/time, 4 times/d), combined with compound chlorhexidine mouthwash (H20064451, specification: 200 mL, twice a day, 10 mL/time). The above measures were adopted to prevent infection post-operation. The postoperative treatment period was two weeks.

Observation indicators

The patients were followed up for 6 months, and the osteogenic ability (osteogenic thickness, osteogenic height, and bone mineral density around implants) at different time points, the success rate of dental implants when suture was removed after operation, and the state indicators around implants before and after treatment were observed. The therapeutic effects of two groups were compared.

Statistical analysis

SPSS statistical software was employed to process and analyze the overall data. The data were described by mean ± standard deviation ($\bar{x}\pm s$) and compared by t test. Contrast between different groups was performed by one-way ANOVA with the significance level set at $P<0.05$.

RESULTS

The results of osteogenic ability between two groups at different times are given in Table I. The experimental results suggested that there was 1 case of implant loosening and 1 case of implant not combining with body bone, and 25 cases survived in controls. In experimental group, the implants were all integrated with the body bone, and 40 cases survived. The width and height of bone formation in experimental group were higher relative to controls ($P<0.01$). After implants covering PRF, the recovery level of bone mineral density in experimental group was higher as against controls ($P<0.05$).

The results of bone resorption level after surgery were compared. The experimental results revealed that as against controls, the treatment of experimental group using implants to cover the PRF had an obvious increase in bone resorption level after immediate implantation ($P<0.05$), and the bone resorption level was higher at 6 months post-surgery than at 3 months post-surgery ($P<0.01$) (Table I).

Table I also shows the results of peri-implant status indicators before and after the treatment. There were no clear differences in dental plaque index (PLI), sulcus bleeding index (SBI), bleeding on probing (BOP), and periodontal probe depth (PD) between two groups pre-treatment ($P>0.05$). Through treatment, the peri-implant status indicators were decreased in different degrees as against controls ($P\leq0.01$).

Table I. Treatment outcomes scores for the patients at before and after the treatment and follow-ups.

Indicators of detection	3 months post operation		6 months post operation	
	Controls (n=27)	Exp. group (n=40)	Controls (n=27)	Exp. group (n=40)
Width of bone formation	3.267±0.134	3.587±0.099	4.375±0.157	4.786±0.102
Height of bone formation	3.693±0.112	4.107±0.108	5.149±0.124	5.597±0.126
Bone mineral density	0.537±0.025	0.601±0.056	0.599±0.023	0.687±0.034
Bone resorption level	0.23±0.09	0.33±0.06	0.15±0.04	0.21±0.02
PLI	4.76±0.46	4.52±0.38	1.70±0.43	0.76±0.32
SBI	4.70±0.72	4.84±0.75	2.36±0.39	1.27±0.34
BOP	9.36±0.77	9.09±0.45	6.37±0.42	3.20±0.25
Periodontal PD	6.99±0.95	7.07±1.21	4.66±0.27	2.12±0.39

PLI, dental plaque index; SBI, sulcus bleeding index; BOP, bleeding on probing; PD, probe depth.

DISCUSSION

With the progress of people's life, the health of teeth has gradually become a problem of great concern to people. The incidence of tooth defects is gradually increasing. The pain of teeth will follow patients all the time. Immediate implant placement can greatly reduce the pain of patients, but the effect of implant on bone defect osteogenesis needs to be further studied.

Maidhof *et al*. (2012) have found that PRP contains many growth factors, which can regulate the tissue engineering intervertebral disc and cartilage formation of human nucleus pulposus. Most scientists believe that the growth factors in PRP can survive for about a week. Studies have shown that the reason that PRP can accelerate bone regeneration in patients with oral bone defects is that the high concentration of growth factors and fibrinogen in PRP can accelerate the formation of fibrous network scaffolds, thereby inducing the growth of new tissue. During the recovery period following dental implantation, the recovery of dental implants is slow due to bone defects (Lim *et al*., 2020). In the study of Lee *et al*. (2020), if the bone defect around the implant is less than 2 mm in diameter, it will heal by itself under the action of blood clots, which will not affect the effect of implant implantation. However, if the diameter exceeds 2 mm, it must be filled to achieve the combination of the implant and soft tissue. Therefore, the key to the success of implant implantation is the filling material used to fill the periodontal bone defect. Passarelli *et al*. (2020) proposed PRF can improve periodontal healing, mainly because PRF contains many growth factors and cytokines, which can promote the proliferation of MC3T3-E1 osteoblasts and improve the ALP activity of osteoblasts. ALP is a marker of early osteoblast differentiation, suggesting that PRF promotes osteoblast differentiation. Promoting osteoblast proliferation and differentiation, osteocalcin (OC) and type I collagen (COL-1) are bone formation biomarkers (Takaya *et al*., 2018; Choi *et al*., 2019; Modi *et al*., 2019), and bone formation, metabolism, and regeneration are regulated by COL-1 and OC genes, which have a direct relationship with calcium availability. PRF can promote the secretion of OC and COL-1 by osteoblasts on β-tricalcium phosphate scaffolds, thereby promoting bone formation. Tooth defect treatment can also use three-dimensional printing bioactive porous titanium alloy scaffolds (3DP-BPTAS) and rhBMP-2/ pla loaded slow-release nanospheres (SRNs) technology, and rhBMP-2/ PLA SRNs is more conducive to the formation of new bone tissue (Wang *et al*., 2022).

PRF, derived from PRP, was invented by Choukroun, a French doctor, in 2001 (Dohan *et al*., 2006; Opri *et al*., 2016; Zhang *et al*., 2019). Platelets contain growth factors that promote healing, so they can improve the healing rate of injured tissues. PRP is the first generation of platelet concentrate products, while PRF is the second generation of platelet concentrate products. Although PRP has the functions of strong repair, hemostasis, etc., PRF is simpler to prepare than PRP. There is no need for any additives in the preparation, which is safer and more natural. In treatment, autologous blood is usually used to prepare PRF, which has the advantages of non-repulsion and high preparation efficiency. Some studies have shown that PRF can combine with β-catenin pathway to promote the differentiation of mouse osteoblasts. In addition, Qin (2021) revealed that β-catenin signaling pathway was related to the proliferation and apoptosis of fibroblast membrane cells. In the preparation of PRF, centrifugal force and centrifugation speed are particularly important for the recovery rate. Studies have reported that the concentration of PRF clot produced by low-speed centrifugation speed is clearly increased, and the platelet distribution is uniform (Miron *et al*., 2020).

When tooth bone defects were filled, due to the limited number of intraoral donors and the high morbidity associated with the use of extraoral donors, and autologous bone also has disadvantages. An alternative to autogenous bone grafting is GBR. First mentioned by Dahlin *et al*. in 1988, the concept is derived from the principle of guided tissue regeneration described by Lindhe *et al*. (1982). GBR makes the patient's wound repair, set up a defense line similar to a mechanical barrier, which can prevent other tissue cells from moving into the wound, so as to effectively protect the differentiation and proliferation process of tissue cells that need healing, and make up for the shortcomings of BRF in practical application (Chatelet *et al*., 2022). The presence of dental implants at a specific time directly stems from the presence of bone, thus enabling their long-term maintenance. Therefore, implant survival is a good way to assess the effectiveness of bone graft as it represents the ultimate goal of treatment planning, and the aim of this article was to examine the effect of PRF combined with GBR on the osteogenic capacity of bone defects around implants.

In addition, the bone width and bone height of experimental group were higher relative to controls ($P<0.01$). The level of bone resorption in experimental group was superior as against controls ($P<0.05$). There was similar between two groups before treatment ($P>0.05$). The PLI, SBI, BOP, and periodontal PD in experimental group were better than those in controls ($P<0.01$). Therefore, patients who received PRF combined with GBR had faster recovery post-surgery and less postoperative pain and discomfort. This may be because PRF can reduce

inflammation and tissue damage, thereby promoting tissue repair and regeneration.

CONCLUSION

The results pointed out that PRF plus GBR could markedly improve the osteogenic ability of bone defects around implants, accelerate the differentiation of osteoblasts, thereby reducing the duration of postoperative recovery and the occurrence of postoperative pain and inflammation in patients. However, further studies are needed to verify its long-term efficacy and safety.

Funding

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IRB approval

This study was approved by the Advanced Studies Research Board of Hebei Provincial Eye Hospital, Xingtai, Hebei Province, 654000, China.

Ethical approval

The study was carried out in compliance with guidelines issued by Ethical Review Board Committee of Hebei Provincial Eye Hospital, China. All procedures were approved by the ethics committee, and all subjects included signed informed consent. For patients right to know, it was necessary to inform patients of the risks of surgical treatment, carry out publicity and education of oral hygiene, and explain the treatment plan in detail to patients during surgery. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Busenlechner, D., Mailath-Pokorny, G., Haas, R., Fürhauser, R., Eder, C., Pommer, B. and Watzek, G., 2016. graftless full-arch implant rehabilitation with interantral implants and immediate or delayed loading-part II: Transition from the failing maxillary dentition. *Int. J. Oral Maxillofac. Implants*, **31**: 1150-1155. https://doi.org/10.11607/jomi.4326

Chatelet, M., Afota, F. and Savoldelli, C., 2022. Review of bone graft and implant survival rate: A comparison between autogenous bone block versus guided bone regeneration. *J. Stomatol. Oral Maxillofac. Surg.*, **123**: 222-227. https://doi.org/10.1016/j.jormas.2021.04.009

Choi, H.K., Kim, G.J., Yoo, H.S., Song, D.H., Chung, K.H., Lee, K.J., Koo, Y.T. and An, J.H., 2019. Vitamin C activates osteoblast genesis and inhibits osteoclast genesis via Wnt/β-catenin/ATF4 signaling pathways. *Nutrients*, **11**: 506-512. https://doi.org/10.3390/nu11030506

Dohan Ehrenfest, D.M., Pinto, N.R., Pereda, A., Jiménez, P., Corso, M.D., Kang, B.S., Nally, M., Lanata, N., Wang, H.L. and Quirynen, M., 2018. The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors, and fibrin architecture of a leukocyte-and platelet-rich fibrin (L-PRF) clot and membrane. *Platelets*, **29**: 171-184. https://doi.org/10.1080/09537104.2017.1293812

Dohan, D.M., Choukroun, J., Diss, A., Dohan, S.L., Dohan, A.J., Mouhyi, J. and Gogly, B., 2006. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part II: Platelet-related biologic features. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.*, **101**: e45-e50. https://doi.org/10.1016/j.tripleo.2005.07.009

Elgali, I., Omar, O., Dahlin, C. and Thomsen, P., 2017. Guided bone regeneration: materials and biological mechanisms revisited. *Eur. J. Oral Sci.*, **125**: 315-337. https://doi.org/10.1111/eos.12364

Fillingham, Y. and Jacobs, J., 2016. Bone grafts and their substitutes. *Bone Joint J.*, **98**: 6-9. https://doi.org/10.1302/0301-620X.98B.36350

Fürhauser, R., Mailath-Pokorny, G., Haas, R., Busenlechner, D., Watzek, G. and Pommer, B., 2016. Patient-perceived morbidity and subjective functional impairment following immediate transition from a failing dentition to fixed implant rehabilitation. *Int. J. Oral Maxillofac. Implants*, **31**: 651-656. https://doi.org/10.11607/jomi.4471

Lee, K.H., Hong, S.H., Jun, J., Jo, Y., Jo, W., Choi, D., Joo, J., Jung, G., Ahn, S. and Kronbichler, A., 2020. Treatment of refractory Henoch-Schonlein Purpura (HSP) with dapsone: A systematic review. *Korean J. Pediatr.*, **115**: 5-7.

Li, X., Yang, H., Zhang, Z., Yan, Z., Lv, H., Zhang, Y. and Wu, B., 2018. Platelet-rich fibrin exudate promotes the proliferation and osteogenic differentiation of human periodontal ligament cells in vitro. *Mol. Med. Rep.*, **18**: 4477-4485. https://doi.org/10.3892/mmr.2018.9472

Lim, H.K., Hong, S.J., Byeon, S.J., Chung, S.M., On, S.W., Yang, B.E., Lee, J.H. and Byun, S.H., 2020. 3D-printed ceramic bone scaffolds with variable pore architectures. *Int. J. Mol. Sci.*, **21**: 6942. https://doi.org/10.3390/ijms21186942

Lindhe, J., Nyman, S. and Karring, T., 1982. Scaling

and root planing in shallow pockets. *J. clin. Periodontol.,* **9**: 415–418. https://doi.org/10.1111/j.1600-051x.1982.tb02054.x

Maidhof, R., Alipui, D.O., Rafiuddin, A., Levine, M., Grande, D.A. and Chahine, N.O., 2012. Emerging trends in biological therapy for intervertebral disc degeneration. *Discov. Med.*, **14**: 401-411.

Miron, R.J., Xu, H., Chai, J., Wang, J., Zheng, S., Feng, M., Zhang, X., Wei, Y., Chen, Y., Mourão, C.F.D.A.B. and Sculean, A., 2020. Comparison of platelet-rich fibrin (PRF) produced using 3 commercially available centrifuges at both high (~ 700 g) and low (~ 200 g) relative centrifugation forces. *Clin. Oral Investig.*, **24**: 1171-1182. https://doi.org/10.1007/s00784-019-02981-2

Modi, P.K., Prabhu, A., Bhandary, Y.P., Shenoy P, S., Hegde, A., Es, S.P., Johnson, R.P., Das, S.P., Vazirally, S. and Rekha, P.D., 2019. Effect of calcium glucoheptonate on proliferation and osteogenesis of osteoblast-like cells *in vitro*. *PLoS One*, **14**: e0222240. https://doi.org/10.1371/journal.pone.0222240

Opri, M., Amzoiu, E., Manolea, H.O. and Rîcă, R., 2016. Computational study of physicochemical properties of the monomers used in stomatology. *Key Eng. Mater.,* **695**: 59-64. https://doi.org/10.4028/www.scientific.net/KEM.695.59

Passarelli, P.C., Romeo, A., Lopez, M.A., De Angelis, P., Desantis, V., Piccirillo, G.B., Papa, R., Papi, P., Pompa, G., Moffa, A. and Casale, M., 2020. Evaluation of the periodontal healing of the second mandibular molar distal site following insertion of PRF in the third molar post extraction alveolus. *J. Biol. Regul. Homeost. Agents*, **34**: 111-118.

Pavlovic, V., Ciric, M., Jovanovic, V., Trandafilovic, M. and Stojanovic, P., 2021. Platelet-rich fibrin: Basics of biological actions and protocol modifications. *Open Med.*, **16**: 446-454. https://doi.org/10.1515/med-2021-0259

Qin, X., 2021. Mirna-203 affected the proliferation and apoptosis of fibroblast synovium cells in rheumatoid arthritis rats by regulating the wnt/b-catenin signaling pathway. *Acta Med. Mediterr.*, **37**: 2873-2877.

Takaya, J., Yamanouchi, S., Kino, J., Tanabe, Y. and Kaneko, K., 2018. A calcium-deficient diet in dams during gestation increases insulin resistance in male offspring. *Nutrients*, **10**: 1745. https://doi.org/10.3390/nu10111745

Tettamanti, L., Andrisani, C., Bassi, M.A., Vinci, R., Silvestre-Rangil, J. and Tagliabue, A., 2017. Immediate loading implants: Review of the critical aspects. *Oral Implantol.*, **10**: 129-139. https://doi.org/10.11138/orl/2017.10.2.129

Wang, F., Liu, J., Liu, J., Zhang, S., Yang, M. and Kang, K., 2022. Comparison of the effects of 3D printing bioactive porous titanium alloy scaffolds and nano-biology for direct treatment of bone defects. *Cell. mol. Biol.*, **68**: 86-95. https://doi.org/10.14715/cmb/2022.68.3.11

Wessing, B., Lettner, S. and Zechner, W., 2018. Guided bone regeneration with collagen membranes and particulate graft materials: A systematic review and meta-analysis. *Int. J. Oral Maxillofac. Implants*, **33**: 87-100. https://doi.org/10.11607/jomi.5461

Zhang, S., Cao, D., Xie, J., Li, H., Chen, Z. and Bao, Q., 2019. Platelet-rich fibrin as an alternative adjunct to tendon-exposed wound healing: A randomized controlled clinical trial. *Burns*, **45**: 1152-1157. https://doi.org/10.1016/j.burns.2019.01.007

Zhang, X. and Zhang, Y., 2018. Application of nano-hydroxylapatite/ collagen and its mineralized composites in bone tissue engineering. *Chin. J. Tissue Eng. Res.*, **22**: 5547-5552.