Management of Collapse Tibial Plateau Fractures Using a Hydroxyapatite-Tricalcium Phosphate Ceramic(ATLANTIK®) and Plate Osteosynthesis

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The treatment of bone defects in complex proximal tibial plateau fractures is a challenging situation and biphasic tricalcium phosphate (BCP) ceramics are considered the most promising alternative to autologous bone graft. The aim of the experimental part was to retrospectively asses the use of Atlantik® BCP (a mixture of 70% Hydroxyapatite and 30% beta-tricalcium phosphate) combined with plate osteosynthesis for management of 27 collapse tibial plateau fractures. All fractures healed after a mean time 2.8 months, while the mean time for disappearance the radiolucent zones between the implanted ceramic and receiving tissue was 15 weeks. We noticed a Neer score of 85 points with no reaction to bone substitute or evidence of biomaterial degradation. The study demonstrated that biphasic ceramic biomaterial Atlantik®, combined with supportive plate osteosynthesis, is an effective synthetic bone substitute due to a fast healing and good quality osseointegration.

Keywords: bone defects, biphasic tricalcium phosphate, hydroxyapatite, radiolucent zones, osseointegration

Proximal tibial fractures are grossly heterogeneous lesions associated with many complications and their prognosis is related to articular comminution with severity of collapse and degree of articular step-off, as well as to osteoporosis, soft tissue envelope and patient's comorbidities [1, 2].

The disadvantages of classic Open Reduction and Internal Fixation (ORIF) with laterally placed plates (skin necrosis, nonunions and infections) [3-5], prompted the introduction of biological techniques with Minimally Invasive Plate Osteosynthesis/MIPO using classic plates [6, 7] or the *ideal* locking plates with monoaxial angular stability type Less Invasive Stabilization System – proximal lateral tibia/LISS-PLT [8, 9]. The last acquisition in angular stability fixation tehniques and design was Locked Compression Plate/LCP with combi-holes and the new Polyaxial Locking Plates that allow screw angulation according to the pattern of comminuted fracture [10, 11].

One of the biggest challenges of the tibial plateau fractures is the successful management of the metaphyseal bone defects which are associated with massive comminution, osteoporosis and reduction techniques. [12-14].

Autografts are still considered the golden standard in treatment of bone defects, even if the literature reports difficulties in graft harvesting and graft availability [13]. The allograft usage involves the infection risk (viral or bacterial) and high costs, while it requires a bone bank with all facilities [15].

For over a century, scientists are trying to discover or synthesize inorganic products that could be used as bone substitutes; these products must provide long lasting bone biocompatibility and must provide bone healing abilities. These bone substitutes must solve the autograft and allograft disadvantages [16-18].

Bone grafting materials are those implants that promotes bone healing by one of the following actions: osteogenesis, osteoinduction and osteoconduction [19-22].

A material is osteogenous when it contains living cells, able to form bone tissue (for

example, autografts of living bone). An osteoinductive material is a biological stimulus which

induces local differentiation of mesenchymal cells from the soft parts in osteoblasts and osteocytes (for example, bone morphogenetic proteins/BMP). An osteoconductive material allows the apposition of a new bone on its surface, acting mainly as a support for the bone tissue (for example, hydroxyapatite, tricalcium phosphate) [19, 23].

Autografts or cancellous autogenous bone grafts, as well as the vascularized cortical ones, can be osteogenous (since they contain living bone cells), osteoinductive (due to the protein matrix), and osteoconductive (due to the mineral bone matrix). These properties also describe the ideal bone substitute. [24] Osseointegration is a term used to describe the biological interaction between the grafted material (graft/implant) and the host in the process of bone healing [15].

Osteoconductive materials became more important especially in bone pathology while they are used as bone substitutes. These substances have a composition similar to the bone mineral matrix and are biocompatible. Their main function is of bone tissue support, allowing bone apposition on their surface; thus, they are used mainly for treating the bone defects [25]. More recently, they are used as a vehicle for osteoinductive substances, augmenting bone formation [28].

While initially, only coral hydroxyapatite, calcium phosphate (Plaster-of-Paris) and then bioactive glasses (bioviotroceramics) were used as bone substitutes,

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nowadays we are using phosphocalcic cements and osteoconductive ceramic materials [29, 30].

Phosphocalcic cements (CPC) consist in one or more calcium phosphates (CaP) soluble in aqueous solutions. Many experimental and clinical studies have used phosphocalcic cements [31, 32].

In the past 80 years, the ceramic materials (phosphocalcic products) were intensively investigated and used in bone repair [33]. The most important property of the phosphocalcic compounds is the water solubility, so as a compound is more resorbable as it is water soluble (e.g. β-TCP) when a compound is less soluble in water and in the bone matrix, it will be less or hard to be resorbed (e.g. HA). The most used compounds in the medical field are represented by the tricalcium phosphates (β-TCP), hydroxyapatite (HA) [34] and biphasic tricalcium phosphates (BCP, a mixture of β-TCP and HA in a variety of ratios) [25].

These materials are biocompatible and osteoconductive ceramics representing synthetic scaffolds which provide structural support for cells and newly formed tissue [26]; these scaffolds act as extracellular matrix for natural process of tissue regeneration [25, 27]. In the same time, the rate of degradation for scaffolds must be comparable with osseous apposition [35].

One of the main disadvantages of biphasic tricalcium phosphate ceramics is their fragility with low fracture resistance which limits their use in cases with high strength; these macroporous ceramics are weaker in bending or torsion comparing to compression [36, 37]. This is the reason for increasing the mechanical strength using osteosynthesis implants [15, 38].

Atlantik® biphasic tricalcium phosphate substitute

Atlantik® (MedicalBiomat, France) is ceramic bone substitute [39] representing a mixture of 70% Hydroxyapatite [$CA_{10}(PO_4)_6(OH)_2$] and 30% beta-tricalcium phosphate [$Ca_3(PO_4)_2$].

This ceramic bone substitute (table 1) is produced in various geometric blocks (70% total porosity, partially interconnected by 300-600 µm pores) as well as ingranular form with a granule diameter of 0.5 mm, 1 mm, 2 mm and 4 mm (70% total porosity, with a minimum pore size 300-600 µm and maximum size 2500-5000 µm. The granular form of Atlantik® must be used in areas with no or low mechanical stress while the blocks will be used in regions with maximal compression stress of 10 MPa. [39]

While a pore size larger than 100 µm is necessary, the optimal interconnection size is still debatable. However, the increasing of porosity content or size strongly decreases the mechanical properties [25, 37, 40].

Exponential functions are used to assess the strength-porosity dependence of ceramics [37]:

$$\sigma_R = \sigma_0 \text{'''} \exp (\text{“ } b \text{'''} p)$$

Where σ_R represent the strength for a volume fraction of pores p (%), and σ_0 represent the strength of the material to porosity.

Observations of micro- and macropores were conducted with a scanning electron microscope (SEM). In figure 1 and figure 2 there are revealed the macroporosity and microporosity, respectively, for Atlantik® substitute with a porogen particle size 300-600 µm [37].

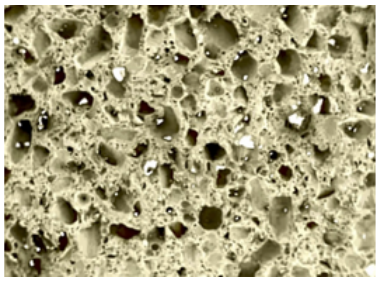

Fig. 1 Atlantik® macroporosity for porogen particle size of 300-600 µm Adapted from [37, 39]

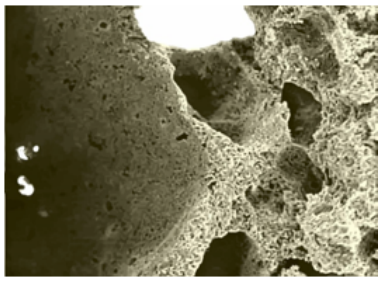

Fig. 2 Atlantik® microporosity for porogen particle size of 300-600 µm Adapted from [37, 39]

The aim of this retrospective study is to assess the use of a macroporous biphasic synthetic bone substitute Atlantik® (MedicalBiomat, France) combined with plate osteosynthesis for management of complex tibial plateau fractures, while exhibiting the biocompatibility, quality and extent of osseous healing.

CHARACTERISTICS	BLOCKS	GRANULATES
CRYSTAL PHASES	HAP: Ca10 (PO4) 6(OH)2= 70 + 5% TCP: Ca3 (PO4) = 30 + 5%	
DIMENSIONS	+ 0,5 mm (except specific shapes)	0.5 mm : 300-600 µm 1 mm : 600-1250 µm 2 mm : 1250-2500 µm 4 mm : 2500 - 5000 µm
%POROSITY	70 + 2%	≈ 70 %
MACROPOROSITY	≈300-600 µm	≈50 -1500 µm
COMPRESSIVE STRENGTH	10MPa	X
ENDOXINES	≤ 20 EU	

Table 1
TECHNICAL CHARACTERISTICS OF ATLANTIK® BONE SUBSTITUTE, ADAPTED FROM [39]

Experimental part

Materials and methods

Our retrospective study was realized between April 2015 – December 2016 in Department of Orthopaedics of Universitary Sf. Spiridon Hospital Iasi and Vaslui County Hospital. A sample of 27 patients with acute tibial plateau fractures were evaluated, 12 males and 15 females with a mean age of 46.5 years (range 22-76 years). Leading causes of the fractures were high-energy traffic accidents and falls. The classification of fractures was realized according to Schatzker and we included 10 fractures type II, 4 fractures type IV, 8 fractures type V, 5 fractures type VI. The imagistic exam included in all cases radiographs of the knee and tibia as well as CT scans with 3D reconstruction for articular comminution and collapse.

All patients were operated with reconstruction of the proximal tibia fracture, augmentation of the bone defect with Atlantik® bone substitute in granular form and osteosynthesis with supportive plate (fig. 3, fig. 4).

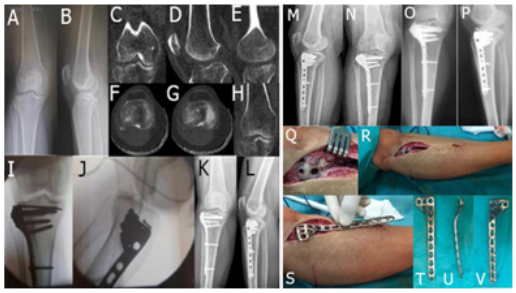

Fig. 3 (**A-V**) Fracture of the lateral tibial plateau type II Schatzker. Plate and bone substitute. (**A, B**) preoperative X-rays; (**C-H**) CT exam; (**I, J**) intraoperative fluoroscopic image with excellent reduction of the articular surface, filling the bone defect with Atlantik® bone substitute, osteosynthesis with 2 Kirschner wires and a locked plate; (**K, L**) X-ray control at 1 month; (**M, N**) X-ray control at 3 months (radiologic evidence of decreasing granular aspect of bone substitute); (**O, P**) X-ray control at 12 months; (**Q**) intraoperative aspect after plate removal with cortical window and osseointegration of the bone substitute; (**R, S**) wounds aspect after plate removal with MIPO incisions and plate position; (**T-V**) aspect and design of a LCP-PLT plate with limited contact.

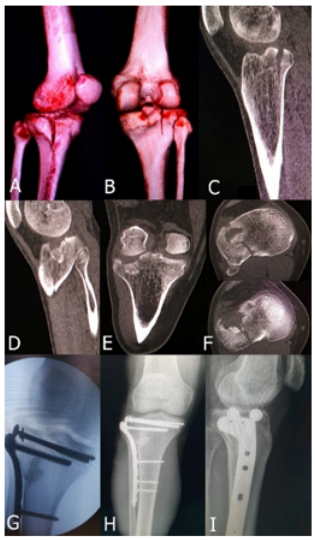

Fig. 4 (**A-I**) Fracture of the lateral tibial plateau type II Schatzker. Plate and bone substitute. (**A, B**) CT exam with 3D reconstruction which reveals the fracture aspect; (**C-F**) sections of CT exam; (**G**) intraoperative fluoroscopic control with excellent articular reconstruction of the fracture: osteosynthesis with 2 cancellous screws and LCP-PLT plate, filling of the bone defect with Atlantik® bone substitute; (**H, I**) X-ray control at 1 month postoperative

Three patients with skin injuries were operated with temporary bridging external fixator while the conversion to a plate fixation and augmentation with bone substitute was realized after 7, 10 and 14 days respectively.

For all patients we have used a lateral curved incision with disinsertion of the anterior tibial muscle 1-2 cm from the tibial ridge for minimally invasive insertion of the plate. Reposition of the articular collapse was realized through a metaphyseal lateral cortical window using a special curved instrument and fluoroscopic control.

The bone defect was augmented with Atlantik® bone substitute according to the *triad of osteoconduction* [13,15]: a. direct apposition of the implant with the surrounding bone; b. viability of the surrounding bone; c. augmentation of the interface between surrounding bone and substitute by internal fixation with plates (we have used classic plates in 10 cases and locked plates in 17 cases).

The patients were immobilized with a fixed orthosis for 2-3 weeks; they started walking without weight-bearing until 6-8 weeks (according to the radiographic results) and rehabilitation after removal the orthosis. Total weight-bearing was allowed at 10-12 weeks post-operatively. The clinical and radiographic follow-up for all patients was recorded for a minimum period of 12 months (average 18,5 months, range 12-28 months). We recorded the quality of articular reconstruction as well as the stability of the construct, the time to fracture healing, the osseointegration of the bone substitute [26], the functional results and rehabilitation according to Neer Score.

Results and discussions

The anatomical reconstruction of the articular surface was recorded with postoperative and follow-up X-rays for 20 patients, while in 7 patients we found minimal secondary displacement (less than 2 mm) due to fracture comminution and osteoporosis.

An uneventful union was present after an average 2.8 months (limits 2-4 months). The radiological aspects as well as the osseointegration of the bone substitute were recorded using 3 important aspects: the zone between ceramic and surrounding bone, the radiological density of the ceramic and ceramic biodegradation [15].

Postoperative X-ray showed radiolucent zones between the implanted ceramic and receiving tissue. Over time, the radiolucent aspect disappeared and new bone developed on the ceramics, due to osteoconductive properties [41]. The mean interval for disappearance of radiological gap was 15 weeks, while the granularity disappeared at 5.5 months with apparent increasing in radiographic density and homogenization.

In the present series, we observed no reactions to ceramic implant, such as wound problems with excessive postoperative drainage, dermatitis, allergic reactions or infections; no obvious evidence of ceramic biodegradation was detected even after 2 years post implantation.

At the most recent follow-up, 6 patients developed secondary mild osteoarthritis signs but there were well tolerated in most of the cases. The mean Range of Motion (ROM) was 118° (range 10° -130°) while the final result was graded with the Neer Score (mean value 85 points, range 70-100 points); we have found 19 excellent and 8 satisfactory results.

Complex articular tibial plateau fractures are difficult to treat and they are associated with a high rate of complications [2, 4]. In difficult cases, primary total knee arthroplasty has potential advantages for elderly patients, while it can be technically challenging in younger patients [42,43]. The management of bone defects associated with

comminution and osteoporosis represents a great challenge in clinical practice [12,38,44].

Bone grafting (autografts, allografts and synthetic substitutes) is an important treatment for bone defects while successful incorporation of grafted biomaterial into bone defects requires the ability and performance of material to promote new bone formation and provide a scaffold for osteogenesis [25,45]. While the autograft techniques have limited resources and the allograft used is restricted due to the spreading of infectious disease, developing the ideal substitute is an actual trend in orthopaedics [15, 24]. The characteristic of an ideal artificial bone material include safety, biocompatibility, excellent biodegrability, ideal porosity, good mechanical properties, osteogenesis, osteoinduction and osteoconduction [24, 46]. Every bone substitute has strengths and weaknesses and no one has demonstrated all the mentioned requirements. Pore diameter and the porosity, which are connected, are important physical parameters for scaffolds since they allow adequate space for cell migration and expansion [25, 47].

A minimum pore size of 100 μm is considered optimal for bone ingrowth, while the pore size more than 200 μm allows the development of mature osteon [25, 48]. Biphasic calcium phosphate (BCP) bone substitutes (HA-β-TCP in a variety of ratios) are considered the most promising alternative to autologous bone graft [37].

In the last years there were investigated a lot of chemical and physical characteristics with important effects in functionality in vivo and in vitro: porosity, grain size and roughness [28, 49]. These studies demonstrated that BCP are biocompatible, bioactive and osteoconductive [41]. The treatment of the most difficult fractures of tibial plateau by plates osteosynthesis was improved with the use of bone substitutes [12-14].

In our institutions, until 2015, we have used for bone defects 2 types of macroporous BCP: Ceraform® (Teknimed, France - a mixture 65% HA, 35% β-TCP) and Eurocer® (FH Orthopedics, France - a mixture 55% HA, 45% β-TCP); we exhibited the efficacy of this ceramics, with a fast and good quality osseointegration, while the osteosynthesis was used in most of the cases. [15]

In the present investigation with Atlantik® bone substitute, we found that grafted ceramic was well incorporated into surrounding host bone; the radiolucent gaps disappeared after a mean time of 15 weeks and these radiological changes represent direct bone apposition to the ceramic implant, due to the osteoconduction [41].

The difficulties of developing new bone substitutes using a single material, prompted the research for preparing composites biomaterials for repairing bone defects [24]. A new biomedical composite with a good similarity to a human bone, a porous nano-hydroxyapatite/polyamide 66 (n-HA/PA66) has been developed in the last years [24, 50].

Calcium phosphate-crystals became ideal drug delivery systems, minimizing the effective dose of the drugs and the side effects. A lot of studies presented the outstanding surface interaction properties of ceramics, which make them appropriate candidates for transporting antibiotics, hormones, bone morphogenetic proteins, vitamins, and oncological drugs [28].

Conclusions

The successful treatment of bone defects in complex tibial plateau fractures is difficult. Ceramic BCP (a mixture of HA and β-TCP in a variety of ratios) are considered the most promising alternative to autologous bone graft.

The retrospective study on 27 collapse tibial plateau fractures demonstrated that biphasic ceramic biomaterial Atlantik®, combined with supportive plate osteosynthesis, is an effective synthetic bone substitute due to a fast healing and good quality osseointegration with no mechanical failures or inflammatory reactions.

References

1.WADDELL JP, JOHNSTON DWC, NEIDRE A. Fractures of the tibial plateau: a review of ninety-ûve patients and comparison of treatment methods, J Trauma, 1981; 21: 376–381;

2.BLOKKER CP, RORABECK CH, BOURNE RB. Tibial plateau fractures: an analysis of the results of treatment in 60 patients, Clin Orthop Relat Res, 1984; 182: 193–199;

3.YOUNG MJ, BARRACK RL. Complications of internal ûxation of tibial plateau fractures. Orthop Rev, 1994; 23: 149–154;

4.MILLS WJ, NORK SE. Open reduction and internal ûxation of high-energy tibial plateau fractures, Orthop Clin North Am, 2002; 33: 177–198;

5.ANISIA EI; CIUNTU, R; CANTEMIR, A; ANTON, N; DANIELESCU, C; NEGRU, R.; BOGDANICI, CM; VASILUTA C; GEORGESCU, STO; SIRBU PD; CIUNTU, BM. The Importance of Fluconazole in Treament of Endogenous Endophthalmitis in Patients Prior Treated Using Negative Pressure Therapy for Wound Closure Contaminated with Methicillin-resistant Staphylococcus aureus, Rev. Chim. (Bucharest), **68**, no. 7, 2017, p. 1598-1601

6.KRETTEK C, GERICH F.T., MICLAU T.H. A minimally invasive medial approach for proximal tibia, Injury, 2001, vol. 32, suppl. 1, 4-13;

7.SIRBU P., MIHAILA R., GHIONOIU G., BRUJA R., ASAFTEI R. Minimally invasive plate osteosynthesis (MIPO) in proximal and distal fractures of tibia, In Smrkolj Vl., (ed.) - 7th European Trauma Congress, Ljubljana (Slovenia), May 14-17, Ed. Medimond Italia, 2006, 349-354;

8.GOESLING T., FRENK A., APPENZELLER A., GARAPATI R., MARTI A., KRETTEK C., LISS PLT: Design, mechanical and biomechanical characteristics, Injury, Int. Care Injured, 2003, S-A 11-15;

9.SIRBU PD, E. CARATA, T. PETREUS, F. MUNTEANU, C. POPESCU, R. ASAFTEI AND P. BOTEZ. Minimally Invasive Surgery by Angular Stability Systems in Proximal Tibia Fractures – Biomechanical Characteristics and Preliminary Results, IFMBE Proceedings, International Conference on Advancements of Medicine and Health Care through Technology; 2009, 26, 413-416;

10.FRIGG R., FRENK A., HAAS N.P., REGAZZONI P.- The Locking Compression Plate System, Dialogue (AO International), 2001,14, I, 8-9;

11.HAIDUKEWYCH G, SEMS SA, HUEBNER D, HORWITZ D, LEVY B. Results of polyaxial locked-plate fixation of periarticular fractures of the knee, , Surgical technique. J Bone Joint Surg Am., , 90 Suppl 2, 2008 Mar, 117-34;

12.BUCHOLZ RW, CARLTON A, HOLMES R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. Clin Orthop Relat Res. 1989 Mar; (240):53-62;

13.NEWMAN JT, SMITH WR, ZIRAN BH, HASENBOEHLER EA, STAHEL PF, MORGAN SJ. Efficacy of composite allograft and demineralized bone matrix graft in treating tibial plateau fractures with bone loss.; Orthopedics, 2008 Jul; 31(7):649;

14.KHODADADYAN-KLOSTERMANN C, LIEBIG T, MELCHER I, RASCHKE M, HAAS NP. Osseous integration of hydroxyapatite grafts in metaphyseal bone defects of the proximal tibia (CT study), Acta Chir Orthop Traumatol Cech., 2002;69(1): 16-21;

15.SIRBU PD, T PETREUS, FL. MUNTEANU, M. PERTEA, S. LUNCA, V. POROCH, P. BOTEZ, Clinical Experience with a Macroporous Synthetic Bone Substituite (Eurocer) in the Treatment of the Patients with Bone Defects. International Conference on Advancements of Medicine and Health Care through Technology IFMBE Proceedings, 2011, Volume 36. Part 5, 358-368;

16.VERNE E, BOSETTI M, BROVARONE CV, MOISESCU C, LUPO F, SPRIANO S, CANNAS M., Fluoroapatite glass-ceramic coatings on alumina: structural, mechanical and biological characterisation.; Biomaterials., 2002 Aug; 23(16): 3395-3403;

17.GISEP A, KUGLER S, WAHL D, RAHN B., Mechanical characterisation of a bone defect model filled with ceramic cements, , J Mater Sci Mater Med., 2004 Oct; 15(10): 1065-1071;
18.RIBEIRO C.C., BARRIAS C.C., BARBOSA M.A., Preparation and characterisation of calcium-phosphate porous microspheres with a uniform size for biomedical applications, J Mater Sci Mater Med., 2006 May; 17 (5): 455-63;
19.EL-GHANNAM A., Bone reconstruction: from bioceramics to tissue engineering.; Expert Rev Med Devices. Review, 2005 Jan; 2(1):87-101;
20.GRAUER JN, BEINER JM, KWON B, VACCARO AR., The evolution of allograft bone for spinal applications.; Orthopedics, Review, 2005 Jun, quiz 578-9.; 28(6):573-577;
21.YAMAMOTO M, TAKAHASHI Y, TABATA Y., Enhanced bone regeneration at a segmental bone defect by controlled release of bone morphogenetic protein-2 from a biodegradable hydrogel.; Tissue Eng., 2006 May; 12(5):1305-11;
22.HIDAKA C, CUNNINGHAM ME, RODEO SA, MAHER SA, ZHU W., Modern biologics used in orthopaedic surgery, Curr Opin Rheumatol. Review, 2006 Jan; 18(1):74-9;
23.PRYOR, LANDON & GAGE, EARL & LANGEVIN, CLAUDE-JEAN & HERRERA, FERNANDO & D BREITHAUPT, ANDREW & GORDON, CHAD & AFIFI, AHMED & ZINS, JAMES & MELTZER, HAL & GOSMAN, AMANDA & R COHEN, STEVE & HOLMES, RALPH.. Review of Bone Substitutes. Craniomaxillofacial trauma & reconstruction. 2009, 2, 151-160;
24.XIONG Y, REN C, ZHANG B, YANG H, LANG Y, MIN L, ZHANG W, PEI F, YAN Y, LI H, MO A, TU C, DUAN H, Analyzing the behavior of a porous nano-hydroxyapatite/polyamide 66 (n-HA/PA66) composite for healing of bone defect, International Journal of Nanomedicine, 2014, Volume 9, Issue 1, 485-494;
25.WONGWITWICHOT P, KAEWSRICHAN J, CHUA KH, RUSZYMAH BH. Comparison of TCP and TCP/HA Hybrid Scaffolds for Osteoconductive Activity, 2010, Open Biomed Eng J.; Epub 2010 Dec 30; 4: 279-285;
26.SIRBU PD, ASAFTEI R, DANCIU M, MIHAILA R, SIMION L, COTRUTZ CE, PETREUS T, BOTEZ P, Experimental Study Regarding the Comparative Behavior of Three Osteoconductive Bone Graft Substitutes, AT-EQUAL 2010: 2010 ECSIS SYMPOSIUM ON ADVANCED TECHNOLOGIES FOR ENHANCED QUALITY OF LIFE: LAB-RS AND ARTIPED, 2010, 27-29;
27.HENCH L.L., POLAK J.M., Third-generation biomedical materials, Science, vol. 295, 2002, 1014-1017;
28.XIDAKI D, AGRAFIOTI P, DIOMATARI D, KAMINARI A, TSALAVOUTAS-PSARRAS E, ALEXIOU P, PSYCHARIS V, TSILIBARY EC, SILVESTROS S, SAGNOU M., Synthesis of Hydroxyapatite, â-Tricalcium Phosphate and Biphasic Calcium Phosphate Particles to Act as Local Delivery Carriers of Curcumin: Loading, Release and In Vitro Studies. Materials (Basel). 2018 Apr 12; 11(4). pii: E595;
29.BAUER TW, MUSCHLER GF. Bone graft materials. An overview of the basic science. Clin Orthop Relat 2000 Res.(371): 10-27;
30.LARSON S., Bone substitutes in the treatment of fracture, in Lemaire R, Bentley J, European Instructional Course Lectures, 2007, 8, 36-41;
31.CONSTANTZ BR, BARR BM, ISON IC, FULMER MT, BAKER J, MCKINNEY L, GOODMAN SB, GUNASEKAREN S, DELANEY DC, ROSS J, POSER RD, Histological, chemical, and crystallographic analysis of four calcium phosphate cements in different rabbit osseous sites., J Biomed Mater, 1998, Res.; 43(4):451-61;
32.FRANKENBURG EP, GOLDSTEIN SA, BAUER TW, HARRIS SA, POSER RD. Biomechanical and histological evaluation of a calcium phosphate cement. J Bone Joint Surg Am., 1998 Aug; 80(8): 1112-24;
33.BOHNER M., Calcium orthophosphates in medicine: from ceramics to calcium phosphate cements, Injury, Int. J. Care Injured, 2000, 31 S-D, 37-47;
34.OHURA K, HAMANISHI C, TANAKA S, MATSUDA N. Healing of segmental bone defects in rats induced by a beta-TCP-MCPM cement combined with rhBMP-2., J Biomed Mater Res; 1999 Feb, 44(2): 168-75;
35.LEE S.H., SHIN H., Matrices and scaffolds for delivery of bioactive molecules in bone and cartilage tissue engineering, Adv. Drug Deliv. Rev., 2007, vol. 59, 339-359;
36.GISEP A. Research on ceramic bone substitutes: current status. Injury.; 33 Review Suppl 2002 Aug, 2:B 88-92;
37.BIGNON A, CHOUTEAU J, CHEVALIER J, FANTOZZI G, CARRET JP, CHAVASSIEUX P, BOIVIN G, MELIN M, HARTMANN D. Effect of micro- and macroporosity of bone substitutes on their mechanical properties and cellular response.; J Mater Sci Mater Med., 2003 Dec; 14(12): 1089-97;
38.GOFF T, KANAKARIS NK, GIANNOUDIS PV. Use of bone graft substitutes in the management of tibial plateau fractures. Injury. 2013 Jan; 44 Suppl 1:S 86-94;
39.***http://www.medicalbiomat.com/index.php/en/products/236-atlantik-genta
40.LIAO C.J., CHEN C.F., J.H. CHEN, S.F. CHIANG, Y.J. LIN, AND K.Y. CHANGE, Fabrication of porous biodegradable polymer scaffolds using a solvent merging/particulate leaching method, J. Biomed. Mater. Res., 2002, vol. 59, pp. 676-681;
41.OGOSE A, HOTTA T, KAWASHIMA H, KONDO N, GU W, KAMURA T, ENDO N. Comparison of hydroxyapatite and beta tricalcium phosphate as bone substitutes after excision of bone tumors. J Biomed Mater Res B Appl Biomater. 2005 Jan 15; 72(1):94-101;
42.SIRBU, P.D., TUDOR, R., BEREA, G., SCRIPCARU, A., CIUBARA, B., BADULESCU, O.V., Bipolar Polyethylene Radial Head Arthroplasty in Posttraumatic Unstable Elbows. Prosthetic design and clinical results, Mat. Plast., **54** , no.2, 2017, p. 298-301;
43.STEVENSON I, MCMILLAN TE, BALIGA S, SCHEMITSCH EH. Primary and Secondary Total Knee Arthroplasty for Tibial Plateau Fractures. J Am Acad Orthop Surg. 2018 Jun 1;26(11):386-395;
44.SIRBU, P.D., TUDOR, R., VERINGA, V., CIUNTU, B.M., RADU, V., CIUBARA, B., BADULESCU, O.V. Strontium Ranelate in the Healing of Fractures Complicated with Delayed Union. It is Really Effective? Rev. Chim.(Bucharest), **68**, no.8, 2017, p.1825-1828;
45.BENEA H, TOMOAIA G, SORITAU O, PASCA RD. A review on the reconstruction of articular cartilage using collagen scaffolds. Rom Biotech Letters. 2016; 21(4):11735-11742;
46.COSTANTINO, P.D., FRIEDMAN, C.D., Synthetic bone graft substitutes. Otolaryngol Clin North Am. 1994; 27(5):1037–1074;
47.THOMPSON R.C., WAKE M.C., YASEMSKI M.J., MIKOS A.G., Biodegradable polymer scaffolds to regenerate organs, Adv. Polym. Sci.,vol.122, 1995, pp. 245-274;
48.BANSAL SANJAY, CHAUHAN VIJENDRA, SHARMA SANSAR, MAHESHWARI RAJESH, JUYAL ANIL, RAGHUVANSHI SHAILENDRA; Evaluation of hydroxyapatite and beta-tricalcium phosphate mixed with bone marrow aspirate as a bone graft substitute for posterolateral spinal fusion Indian J Orthop. 2009 Jul-Sep; 43(3): 234–239;
49.MATE SANCHEZ DE VAL, J.E.; CALVO-GUIRADO, J.L.; GOMEZ-MORENO, G.; PEREZ-ALBACETE, C.; MAZON, P.; DE AZA, P.N. Inûuence of hydroxyapatite granule size, porosity and crystallinity on tissue reaction in vivo. Part A: Synthesis, characterization of the materials and SEM analysis. Clin. Oral Implants Res. 2016, 27, 1331–1338;
50.YANG AP, LI H, LI JD, LI YB, YAN YG, XIANG HZ. Fabrication of porous n-HA/PA66 composite for bone repair. Key Engineering Materials. 2007; 330:321–324.

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