CZU: 611.018.4 DOI: 10.46727/c.13-14-10-2023.p17-24

CHALLENGES AND SOLUTIONS IN BONE TISSUE ENGINEERING

PROVOCĂRI ȘI SOLUȚII ÎN INGINERIA ȚESUTULUI OSOS

JIAN Mariana[1-4], ORCID 0000-0001-9352-5866
FICAI Denisa[1,2,5], ORCID 0000-0003-1243-6904
NACU Viorel[4,6], ORCID 0000-0003-2274-9912
FICAI Anton[1-3,7], ORCID 0000-0002-1777-0525

[1] Science and Engineering of Oxide Materials and Nanomaterials, Faculty of Applied Chemistry and Materials Science, University POLITEHNICA of Bucharest, Gh. Polizu 1-7, 011061 Bucharest, Romania (*anton.ficai@upb.ro);
[2] National Research Center for Food Safety, University POLITEHNICA of Bucharest, Splaiul Independentei 313, 060042 Bucharest, Romania;
[3] National Center for Micro and Nanomaterials, University POLITEHNICA of Bucharest, Splaiul Independentei 313, 060042 Bucharest, Romania;
[4] Laboratory of Tissue Engineering and Cell Cultures, Nicolae Testemitanu State University of Medicine and Pharmacy, Stefan cel Mare street 165, Chisinau, Moldova (viorel.nacu@usmf.md)
[5] Department of Inorganic Chemistry, Physical Chemistry and Electrochemistry, Faculty of Applied Chemistry and Materials Science, University POLITEHNICA of Bucharest, Gh. Polizu 1-7, 011061 Bucharest, Romania.
[6] Human Cells and Tissue Bank, Traumatology and Orthopedy Clinic Hospital, Stefan cel Mare street, 190, Chisinau, Moldova
[7]Academy of Romanian Scientists, Ilfov Street 3, 050044 Bucharest, Romania;

Abstract: The present work is focused on presenting the challenges and the recent advances in the field of Bone Tissue Engineering. It has to mention that worldwide, the need of bone grafting materials is only exceeded by the need of blood. Some of the most relevant materials used in bone grafting will be presented considering the compositional and morphological similitude with the bone but also the specific needs associated with different pathologies.
Keywords: bone grafts; bone diseases; composite materials; collagen; hydroxyapatite; active agents; drug delivery

Introduction

Bone is a special composite tissue with several major functionalities: mechanical support and protection, movement, mineral storage and homeostasis of some specific ions (Ca^{2+}, PO_4^{3-}, Na^+, Cl^- but also pH/H_3O^+ at the bone level) [1]. Unfortunately, it is highly exposed to specific diseases of congenital or developed due to the daily activity. If the bone mass loss is consistent, in this case bone grafting materials have to be used to assist the healing. Statistically speaking, about 49% of the annual need of grating materials is represented by the bone grafting materials followed by the grafting materials for blood vessels - 11%; nerves – 10%, skin – 9%, etc. [2].

A wide range of materials are used in bone grafting (some representative examples are presented in Table 1) but, considering the composite nature of the bone, mainly composed by hydroxyapatite and collagen, there are many bone grafting materials based on these components, alone or in association with other components. Worth mentioning that according to the classification of the materials used in bone grafting, the composite materials represent the 3rd generation of materials and by improving them, by loading them with cells or cell derived agents (bone morphogenic proteins, growth factors, etc.) the overall performances of the composite materials can be further improved and these tissue engineered composite represents the fourth generation of materials [3]. Nowadays, considering the advance of the additive manufacturing, the more control in developing the materials, it is obvious that the properties of the grafts are better and this is why there is a new trend to consider the materials obtained by additive manufacturing to be the materials of the fifth generation and, also in this case, a major focus is on the nanocomposites.

Table 1. Most representative materials used in bone grafting materials

Inorganic materials	**Organic materials, mainly polymers**
CaPs (especially HA, TCP); $CaSO_4$, $CaCO_3$, bioglasses; (mesoporous) silica; ZrO_2, Al_2O_3, MOFs; zeolites; etc.	**collagen,** gelatin, fibrin, silk fibroin, chitosan, alginate, cellulose, agarose, hyaluronic acid, PEO, PVA, PLA, PLGA, PCL, PHB, etc.

calcium phosphates: CaPs; hydroxyapatite: HA; tricalcium phosphate: TCP; metal-organic frameworks: MOFS; polyethylene oxide: PEO; polyvinyl *alcohol: PVA; poly-L-lactic acid: PLA; poly(lactic-co-glycolide): PLGA; poly(ε-caprolactone): PCL; poly(3-hydroxybutyrate): PHB.*

The aim of this paper is to review some of the most important challenges associated with the composite materials based on collagen and hydroxyapatite from the point of view of regenerative but also curative point of view, when loaded with specific biological active agents.

Collagen/Hydroxyapatite composite materials for bone tissue regeneration

Collagen/Hydroxyapatite composite materials are usually obtained by mineralization of the collagen structures (gel, matrices, fibers) using adequate precursors, soluble or partially soluble calcium salts and soluble phosphates. It is worth to mention that the final properties of the composite materials are strongly related to the mineralization conditions but also a key role is played by the collagen precursor. Considering the high impact of the porosity on the performances of the grafting materials: osteointegration, bioactivity; release, mechanical properties, etc., many researchers, depending on the final application, are focusing on developing materials with controllable porosity. In general, collagen gel is the most versatile form, starting with it, porous or dense mineralized structures can be easily obtained while, starting from the collagen matrix, the porosity will be slightly decrease but usually more porous mineralized structures are obtained (Figure 1).

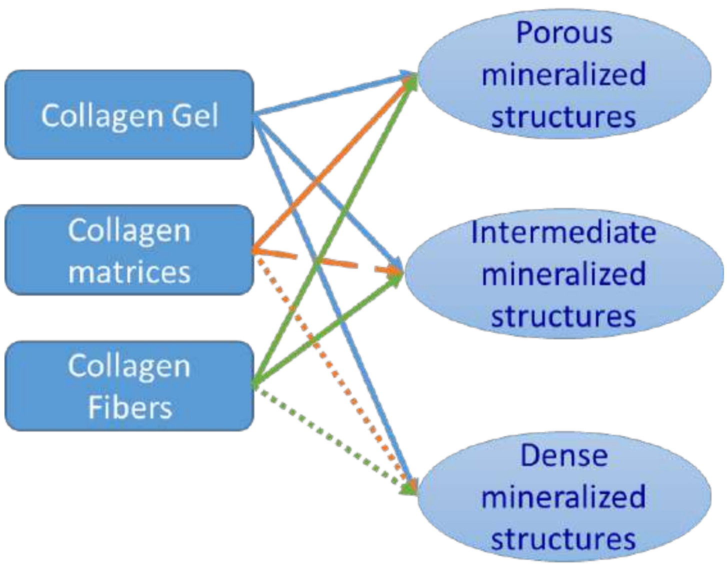

Figure 1. Collagen precursor – porosity correspondence

Considering the various diseases associated with the bone tissue, such as infections or osteoporosis, and the derived increased fracture risks, different materials were developed having antimicrobial or antiosteoporotic properties. Such materials can be obtained by using materials with intrinsic activity, such as for instance chitosan, or doped hydroxyapatite (with Ag^{+} or Zn^{2+}) [4] or even with the addition of Ag, ZnONPs – for inducing antimicrobial activity or Zn, Sr - doped HA for enhancing the cellular activity of the osteoblast and thus to improve the osteo-formation / osteo-resorption ratio.

COLL/HA composite drug delivery systems

The properties of the COLL/HA composite materials can be tuned very well by loading them with adequate biological active agents. It is worth to mention that there are a lot of natural and synthetic agents which are currently used to enhance or even to induce the desired activity, including the fast healing or the treatment of different diseased associated with bone, as presented in Figure 2.

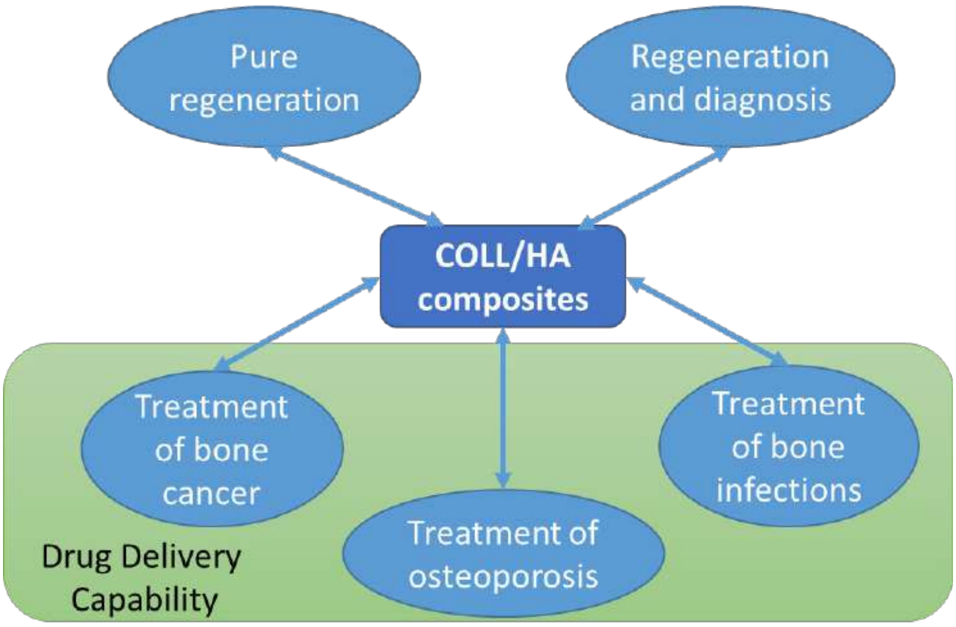

Figure 2. Common applications of COLL/HA composites

A special concern in this case is related to the delivery profile because the release of the active agent has to be in the therapeutical level, for a specific period of time. A major challenge in developing these drug delivery systems is related to the control of the delivery of the active agents to assure a personalized approach, and thus to assure the optimal amount of the active agent, over the exact period of time needed. This control can be thus obtained considering internal but also external triggering factors, pH, light, magnetic field, temperature being some of the most used triggering factors used in such applications [5].

Fast healing can be also achieved starting from COLL/HA composite materials by loading with cells, growth factors, bone morphogenic proteins, vitamins, etc. [6-9].

The treatment of the primary bone cancer involves chemotherapy, surgery and radiotherapy. Depending on the medical recommendation, the order of the chemotherapy and surgery can vary but, during the surgery step, instead of the resected tumoral tissue, multifunctional grafts can be implanted, these grafts being able to assure antitumoral activity (at short-term) and also to assist the healing (at long-term). The antitumoral activity can be assured by multiple mechanisms, by hyperthermia (generated by the presence of magnetite when exposed to proper pulsatory fields), by chemotherapy – cytostatics release or by phototherapy. Moreover, these mechanisms can be synergically applied and in this case, an externally controlled antitumoral activity can be achieved [10].

Antimicrobial bone grafts are developed to be used in already existent infected defects but, they can be also developed to prevent infections as a consequence of the surgical intervention. Depending on the need, antibiotics can be loaded to treat infections associated with the bone tissue while for preventive purpose, especially nanoparticles (such as AgNPs or ZnO NPs) or natural compounds (such as volatile oils, polyphenols, etc.) can be used [11-15].

Table 2. Drug delivery systems used in bone tissue engineering

Fast healing	COLL/HA/b-FGF [6] COLL/HA/BMP-2 [7]
Antitumoral systems	HA-Curcumin [19] COLL/HA/cytostatics [10, 20, 21]
Antimicrobial systems	COLL/HA/antibiotics [11-13] COLL/HA/AgNPs [14] COLL/HA/essential oils [15]
Anti-osteoporotic systems	PLGA/HA/vitamin D3 [16] PCL/PEG/HA/bisphosphonates [17]

In osteoporosis, there are two mechanisms of action of the drugs, some are reducing the resorption rate while others are enhancing bone formation. The healing of the osteoporotic bones is challenging because the bone formation is inferior as the resorption and even during the healing of fractures, the organism can just marginally improve the formation rate. In such situations, the use of specific DDS is needed and specific drugs are loaded, including vitamins, bisphosphonates, strontium ranelate, etc. [16-18].

Conclusions

Bone tissue engineering is a complex field of research which involve pure regeneration, diagnosis and treatment of specific bone related diseases such as osteoporosis, osteomyelitis, osteosarcoma, etc. Considering the composite nature of the bone tissue, the morphology-induces properties of the bone tissue, the most biomimetic solution is based on COLL/HA composite materials and their properties can be further enhanced by loading with different biological active agents – from ions, to ternary oxides, polymers, nanostructures or drugs. Based on the literature screening, many drug delivery systems were presented, some of them being able to assure smart drug delivery in a triggered way, the triggering factor being internal but also of external nature (proper electromagnetic fields generating hyperthermia, or light – generating photothermia, etc.).

References

1. ZHANG X.R., CUI J.J., CHENG L.M., LIN K.L. Enhancement of osteoporotic bone regeneration by strontium-substituted 45S5 bioglass via time-dependent modulation of autophagy and the Akt/mTOR signaling pathway, J Mater Chem B 9(16) (2021) 3489-3501.
2. CHEN C., XI Y., WENG Y., Progress in the Development of Graphene-Based Biomaterials for Tissue Engineering and Regeneration. , Materials 15(6) (2022).
3. MURUGAN R., RAMAKRISHNA S., Development of nanocomposites for bone grafting, Compos Sci Technol 65(15-16) (2005) 2385-2406.
4. BECERRA J., RODRIGUEZ M., LEAL D., NORIS-SUAREZ K., GONZALEZ G., Chitosan-collagen-hydroxyapatite membranes for tissue engineering, Journal of Materials Science: Materials in Medicine 33(18) (2022).

5. TARABUȚA P.A., MOTELICA L., FICAI D., OPREA O., FICAI A., ANDRONESCU E., Drug Delivery Systems for Tissue Engineering, in: O. Gunduz, C. Egles, R.A. Pérez, D. Ficai, C.B. Ustundag (Eds.), Biomaterials and Tissue Engineering, Springer2023, pp. 205-238.
6. HOSHI M., TAIRA M., SAWADA T., HACHINOHE Y., HATAKEYAMA W., TAKAFUJI K., TEKEMOTO S., KONDO H., Preparation of Collagen/Hydroxyapatite Composites Using the Alternate Immersion Method and Evaluation of the Cranial Bone-Forming Capability of Composites Complexed with Acidic Gelatin and b-FGF, Materials 15(24) (2022).
7. WALSH D.P., RAFTERY R.M., CHEN G., HEISE A., O'BRIEN F.J., CRYAN S.-A., Rapid healing of a critical-sized bone defect using a collagen-hydroxyapatite scaffold to facilitate low dose, combinatorial growth factor delivery, Tissue Engineering and Regenerative Medicine 13(10) (2019) 1843-1753.
8. MO X., ZHANG D., LIU K., ZHAO X., LI X., WANG W., Nano-Hydroxyapatite Composite Scaffolds Loaded with Bioactive Factors and Drugs for Bone Tissue Engineering, Int J Mol Sci 24 (2023) Art. No. 1291.
9. NEACSU I.A., ARSENIE L.V., TRUSCA R., ARDELEAN I.L., MIHAILESCU N., MIHAILESCU I.N., RISTOSCU C., BLEOTU C., FICAI A., ANDRONESCU E., Biomimetic Collagen/Zn2+-Substituted Calcium Phosphate Composite Coatings on Titanium Substrates as Prospective Bioactive Layer for Implants: A Comparative Study Spin Coating vs. MAPLE, Nanomaterials-Basel 9(5) (2019).
10. FICAI D., SONMEZ M., ALBU M.G., MIHAIESCU D.E., FICAI A., BLEOTU C., Antitumoral materials with regenerative function obtained using a layer-by-layer technique, Drug Des Dev Ther 9 (2015) 1269-1279.
11. CIOCILTEU M.V., FILIP O.L., MANDA C.V., NICOLAESCU O.E., NEACSU I.A., FICAI A., BUZATU I.M., NICOLICESCU C., CROITORU O., NEAMTU J., Physico-Chemical Characterization and Antibacterial Activity of a Controlled Collagen-Hydroxyapatite-Ciprofloxacin Release System, Farmacia 68(6) (2020) 1055-1061.
12. IONESCU O., CIOCILTEU M.V., MANDA C.V., NEACSU I.A., FICAI A., AMZOIU E., STIOLICA A.T., CROITORU O., NEAMTU J., Bone - Graft Delivery Systems of Type PLGA-gentamicin and Collagen - hydroxyapatite - gentamicine, Mater Plast 56(3) (2019) 534-537.

13. RUSU L.C., NEDELCU I.A., ALBU M.G., SONMEZ M., VOICU G., RADULESCU M., FICAI D., FICAI A., NEGRUTIU M.L., SINESCU C., Tetracycline Loaded Collagen/Hydroxyapatite Composite Materials for Biomedical Applications, J Nanomater 2015 (2015).
14. PATRASCU J.M., NEDELCU I.A., SONMEZ M., FICAI D., FICAI A., VASILE B.S., UNGUREANU C., ALBU M.G., ANDOR B., ANDRONESCU E., RUSU L.C., Composite Scaffolds Based on Silver Nanoparticles for Biomedical Applications, J Nanomater 2015 (2015).
15. FLOREA A.D., DANILA E., CONSTANTINESCU R.R., KAYA M.A., KAYA A.D., COARA G., ALBU L., CHELARU C., Composite scaffolds for bone regeneration made of collagen/ hydroxyapatite/ eucalyptus essential oil, ICAMS 2018 – 7th International Conference on Advanced Materials and Systems, 2018, pp. 93-98.
16.. IGNJATOVIC U.V., AJDUKOVIC Z., USKOKOVIC D. , Multifunctional hydroxyapatite and poly(d,l-lactide-co-glycolide) nanoparticles for the local delivery of cholecalciferol. , Mat Sci Eng C-Bio S 33 (2013) 943–950.
17. RAJAN R.K., CHANDRAN S., SREELATHA H.V., JOHN A., PARAMESWARAN R., Pamidronate-Encapsulated Electrospun Polycaprolactone-Based Composite Scaffolds for Osteoporotic Bone Defect Repair, Acs Appl Bio Mater 3 (2020) 1924–1933.
18. CODREA C.I., CROITORU A.M., BACIU C.C., MELINESCU A., FICAI D., FRUTH V., FICAI A., Advances in Osteoporotic Bone Tissue Engineering, J Clin Med 10(2) (2021).
19. NEACSU I.A., MATEI L., BIRCA A.C., NICOARA A.I., ENE V.L., DRAGU L.D., FICAI A., BLEOTU C., ANDRONESCU E., Curcumin - Hydroxyapatite Systems Used for Bone Cancer Treatment, Revista Romana De Materiale-Romanian Journal of Materials 51(4) (2021) 505-513.
20. MARQUES C., FERREIRA J.M.F., ANDRONESCU E., FICAI D., SONMEZ M., FICAI A., Multifunctional materials for bone cancer treatment, Int J Nanomed 9 (2014) 2713-2725.
21. ANDRONESCU E., FICAI A., GEORGIANA M., MITRAN V., SONMEZ M., FICAI D., ION R., CIMPEAN A., Collagen-hydroxyapatite/Cisplatin Drug Delivery Systems for Locoregional Treatment of Bone Cancer, Technol Cancer Res T 12(4) (2013) 275-284.