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Review

Historical Review of Biological Apatite Crystallography

Toshiro Sakae[1] , Hiroshi Nakada[2] and John P. LeGeros[3]

[1] *Department of Histology, Nihon University School of Dentistry at Matsudo, Chiba, Japan*
[2] *Department of Removable Prosthodontics, Nihon University School of Dentistry at Matsudo, Chiba, Japan*
[3] *Department of Biomaterials and Biomimetics, New York University College of Dentistry, New York, USA*

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Abstract: Biological apatites composing the inorganic part of many hard tissues have many characteristics differing from mineral and/or synthetic apatites. Before the modern precise analytical technique and methods were introduced to the hard tissue study, the non-stoichiometry of biological apatites was a problem, and the carbonated apatite in bone and tooth was sometimes mistaken for a mixture of calcium carbonates, calcium phosphates, and calcium oxides. Apatite is a mineral group which makes wide ranged solid-solution systems. Although hydroxyapatite is the most stable phase in the mimetic conditions to body system among the calcium phosphates, it can not be successfully precipitated under laboratory conditions. Therefore, some mechanisms have been proposed to crystallize biological apatite in the body conditions. In this review, the history of unveiling the nature of biological apatites is described from a crystallographic viewpoint, and bio-medical applications of calcium phosphates are introduced.

Key words: Calcium phosphate, Precursor, Tooth enamel, Dentin, Bone

Introduction

Biological apatites, composing the inorganic part of many hard tissues with the wide distribution from vertebrate bone and tooth to invertebrate Brachiopod Lingula shell[1-3], have many characteristics differing from the mineral and/or synthetic apatites[4]. The terms of "Biomineral" and "Biomineralization" were firstly used by Oomori for the pearl[5]. And the terms of "calcification" and "mineralization" were used as the same meanings in this paper, though there are some controversies for the use of these terms. Before the modern precise analytical technique and methods had been introduced to the hard tissue study, the nonstoichiometry of biological apatites was the arduous problem[6]. These confusion or turmoil was caused from the unique wide variability of apatite crystal itself[7,8]. Therefore, it was unavoidable even if it mistaken the carbonated apatite in bone and tooth as the mixture of calcium carbonate, calcium phosphate, and calcium oxide[9-14].

Before access to the crystallography of apatite and biological apatite in this content, it should be clarified what is crystal. Because, at the formation stage of hard tissues there is a discussion for a long time lasting about the presence of amorphous, or noncrystalline, materials[15-23]. The "amorphous" problem in hard tissues was discussed together with the "precursor" problem in the latter part. Among the wide ranged calcium phosphate components, only orthophosphate, PO_4^{3-}, occurs in the normal human body system, and the other types such as diphospate, $P_2O_7^{4-}$, triphosphate, $P_3O_{10}^{5-}$, tetraphosphate, $P_4O_{13}^{6-}$, pentaphosphate, $P_5O_{16}^{7-}$, and the other condensed chained phosphates were not found[8].

This review briefly describes the history of resolving the "Apatite Problem" in mineralogy and also the "Biological apatite Problem" in the biomineralogy, in concern with the variety of calcium phosphates and apatites. The history of biological apatite was described with the study of the x-ray diffraction (XRD) which is the most powerful and reliable method for crystallographic analysis[24], and the other modern analytical instruments such as Fourier Transform InfraRed (FTIR), Fourier Transform Raman (FT Raman) spectroscopy which are the powerful and reliable methods for molecular structure analysis[25], and some elemental analysis techniques.

Calcium phosphates are the essential minerals for human body not only for the skeletal system but for the homeostasis of mineral balance in body. At the last part, the biomedical applications of apatite and calcium phosphates were briefly reviewed with special remarks on R. Z. LeGeros, she and her colleague firstly proved biological apatite as carbonateapatite.

Apatite Crystallography and X-ray Diffraction Analysis

Mineral Apatite Group, and Etymology of "Apatite"

Corresponding to: Dr. Toshiro Sakae, Department of Histology, Nihon University School of Dentistry at Matsudo, 28701 SakaechoNishi, Matsudoshi, Chiba, 271-8587 Japan; Tel & Fax: +81473609323; Email: sakae.toshiro@gmail.com

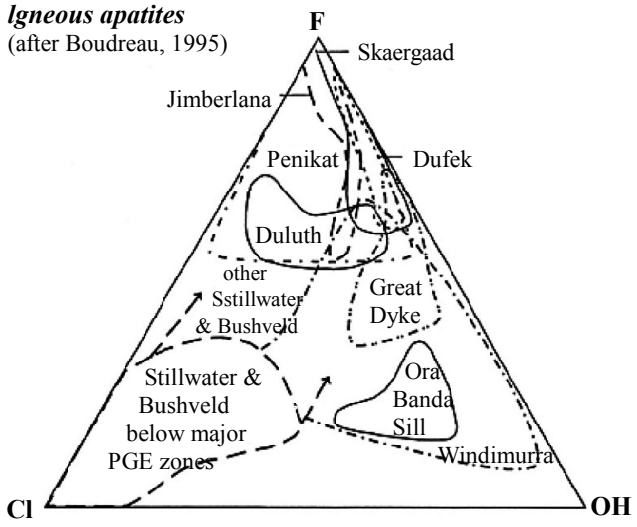

Figure 1. F-OH-Cl solid-solution diagram for the apatite minerals occurred in igneous rocks [30]

Apatite is the most abundant of the phosphatic minerals and consequently is of great importance to industry as the phosphorus containing compounds[8]. Apatites are found in the variety of occurrences in nature; in ignious rocks, metamorphic rocks, sedimentary rocks, meteorites as well as in many biological origins including fossils[6,26,27].

Apatite was named from the Greek "απαταω", to decieve, because of the older mineralogists having referred wrongly it to aquamarine, chrysolite, amethyst, flour, schorl, etc. showing the variety in color and morphology[7]. "Asparagus stone" from Spain was one of the strangely named examples, and "Osteolite" was named for those found in the fossil bones. "Collophane" as carbonate hydroxyapatite, "Stafferite" as francolite, and the other old names are still used at now.

Apatite group has the chemical formula of $M_{10}(XO_4)_6Z_2$, where M = Ca, Sr, Ba, Cd, Pb, etc., X = P, As, V, Mn, Cr, etc., and Z = OH, F, Cl, Br, etc.[6]. The name "apatite" describes a family of compounds having similar structure (hexagonal crystal system, space group, $P6_3/m$) in spite of a wide range of composition[4,28,29]. The apatite series makes a unique solid-solution system; for example, hydroxyapatite, HAp $Ca_{10}(PO_4)_6(OH)_2$, and fluorapatite, FAp $Ca_{10}(PO_4)_6F_2$, making a perfect solidsolution system (Fig. 1)[30,31]. It is notable that the nomenclature of hydroxyapatite valid from the terminal composition, $Ca_{10}(PO_4)_6(OH)_2$, to the midpoint, $Ca_{10}(PO_4)_6FOH$, in the OH-F solid solution system.

Therefore, the slightly substituted F for OH apatite might not be called as flourapatite, which sometimes misused in some international medical and dental journals.

Table 1[6-8,32-34] list the major apatite group minerals with the unit cell dimensions, which are useful to identify the mineral species and/or estimation of the substituted ions. Based on the wide range substitution system of apatite, the included elements, i.e. rare earth elements, have some important information such as geological chronology, environmental geology, geothermometry, etc.[35-37].

Crystal Structures of Apatite and Related Calcium Phosphates

Before the exact apatite crystal structure had been solved, the apatitic Xray patterns were found in tooth and bone mineral[39,40]. In 1930, NaraySzabo[41] and Mehmel[42] determined the crystal structure of FAp and HAp, respectively. However, it was observed that many calcium phosphates with low Ca/P ratio precipitated from solution give the X-ray diffraction pattern of HAp but depart from the ideal stoichiometry, $Ca_{10}(PO_4)_6(OH)_2$[43]. In 1964, the precise crystal structure of HAp was determined[44]. In 1969, the refinement of the naturally occurred HAp was performed[45], and in 1980, fine apatite crystal structure characterization from gravimetrically separated human teeth was achieved by the Reitveld analysis of X-ray data[46].

In the HAp crystal structure, there are two sites for calcium ions, namely Ca(I) and Ca(II). The Ca(I) is called as the columnar Ca, and the Ca(II) the screw axis Ca (Fig. 2). The screw axis Ca makes the calcium triangle, and then the calcium tunnel, in which the OH ions locate. Based on this structural configuration, the OH ions easily substitute with F ions, and the OH ions in tooth enamel are easily released by attack of acids resulted in tooth decay (Fig. 3).

For the more information of the calcium phosphates and apatite crystal structure, refer the references[47-52], and it may be worth to introduce the techniques and methods for hard tissue research[53-62].

Calcium Phosphate Precursors of Apatite

There are some solid phases of calcium phosphate that have been linked to biological mineralization (Table 2). HAp is universally recognized as the final solid mineral phase of bone and teeth[6,64]. The other calcium phosphates have been implicated as minor or precursor phases; they are acid stable and will convert to the thermodynamically stable and insoluble HAp at a high pH (Fig. 4). HAp is stable at neutral or basic pH[65]. Tricalcium phosphate, TCP, needs Mg ion for its formation at room temperature. Both dicalcium phosphate dehydrate, DCPD, or dicalcium phosphate, DCP, and octacalcium phosphate, OCP, have acid phosphate groups (HPO4) and a structural plane on which HAp can be grown epitaxially[66,67].

These hypotheses may explain the dominant morphology of bone apatite is platelets[68] and also in tooth enamel[69]. The formation mechanism of platelike crystals in the mineralized collagen fibrils is not fully understood. One possible explanation is that crystal growth occurs via an OCP intermediate (Fig. 5)[67,70]. OCP has almost the same crystal structure as HAp but contains an extra hydrated layer that may be responsible for the observed plateshaped crystals in natural bone. Amorphous calcium

Table 1. Apatite Group Minerals[6-8, 31-34)]

Chemical name *mineral name*	Idealized chemical formula	Unit cell dimensions axis (Å), angle (°)	Strong X-ray diffraction peaks	Powder Diffraction File (PDF) (JCPDS card no.)
Hydroxyapatite HAp (Hexagonal)	$Ca_{10}(PO_4)_6(OH)_2$	a = 9.41, c = 6.88	2.814 (100) 2.778 (60) 2.720 (60)	9-432
Hydroxyapatite (Monoclinic)	$Ca_{10}(PO_4)_6(OH)_2$	a = 9.445, b = 18.853, c = 6.8783, β = 120	2.817 (66) 2.724 (79) 2.267 (100)	
Fluorapatite FAp	$Ca_{10}(PO_4)_6F_2$	a = 9.3973, c = 6.8782	2.800 (100) 2.702 (60)	15-876
Chlorapatite	$Ca_{10}(PO_4)_6Cl_2$	a = 9.5979, c = 6.7762	2.853 (100) 2.770 (100) 1.960 (50)	12-263
Oxyapatite	$Ca_{10}(PO_4)_6O$	a = 9.38, c = 6.93		
Pyromorphite	$Pb_{10}(PO_4)_6Cl_2$	a = 9.987, c = 7.33	2.99 (100) 2.96 (100) 2.89 (60)	19-701
Dahllite *carbonate apatites*	$Ca_{10}(PO_4)_5(CO_3)(OH)_2$	a = 9.419, c = 6.886	2.811 (80) 2.717 (100) 2.261 (35)	21-145
Francolite	$Ca_{10}(PO_4)_5,(CO_3)F_2$	a = 9.346, c = 6.887	2.79 (55) 2.692(100) 2.24 (45)	31-267
Alforsite	$Ba_{10}(PO_4)_6Cl_2$	a = 10.25, c = 7.64	3.06 (100) 2.13 (40) 2.03 (30)	35-691
Fermorite	$(Ca,Sr)_{10}(AsO_4,PO_4)_6(OH,F)_2$		3.49 (50) 2.86 (100) 2.75 (60)	14-215
Whitlockite	$Ca_{18}Mg_2(PO_4)_{12}[PO_3(OH)]_2$	a = 10.357, c = 37.077	3.1845 (59) 2.8604 (100) 2.5893 (73)	(syn. 9-169)
Mimetite	$Pb_{10}(AsO_4)_6Cl_2$	a = 10.250, c = 7.454	3.06 (100) 3.01 (95) 2.96 (65)	19-683
Chlorellestadite (*Ellestadite*)	$Ca_{10}(SiO_4)_3(SO_4)_3Cl_2$	a = 9.491, c = 6.921	2.84 (100) 2.74 (60) 1.85 (50)	25-173
Britholite	$Ca_4(Ca,Ce)_6(SiO_4,PO_4)_6(OH,F)_2$	a = 9.63, c = 7.03	3.48 (80) 2.836 (100) 2.809 (80)	31-892

phosphate, ACP, was also found to spontaneously precipitate to apatite at physiological conditions[16,71-76)] (Fig. 6). Although many studies searching OCP *in vivo* had been failed[17,77-78)], the improved methods of imaging and structure determination have since led to the identification of stable and transient forms of amorphous precursors in biomineralization of bone and teeth[8,18,19,22,79)]. The

Table 2. Calcium phosphates Candidates for the Precursor of Apatite Formation [63]

	Chemical composition	Ca/P ratio	JCPDS card
Octacalcium phosphate (OCP)	$Ca_8H_2(PO_4)_6 \cdot 5H_2O$	1.33	26-1056
hydroxyspodiosite	$Ca_2PO_4(OH) \cdot 2H_2O$	2.00	
Teracalcium phosphate	$Ca_3(PO_4)_2 \cdot CaO$	2.00	
Tricalcium phosphate (TCP)	$Ca_3(PO_4)_2$	1.50	9-167
α-TCP (high temp. type)			9-348
β-TCP (low temp. type)			
Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4 \cdot 2H_2O$	1.00	9-77
Brushite			11-293
Calcium phosphate-sulfate hydrate *Ardealite*	$CaHPO_4 \cdot CaSO_4 \cdot 4H_2O$	0.50	41-585
Dicalcium phosphate hemihydrate (DCPh)	$CaHPO_4 \cdot 1/2H_2O$	1.00	
Dicalcium phosphate (DCP) Monetite	$CaHPO_4$	1.00	9-80
Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2 \cdot H_2O$	0.50	9-347
Monocalcium phosphate (MCP)	$Ca(H_2PO_4)_2$	0.50	9-390
Amorphous calcium phosphate	$Ca_9(HPO_4)_6(OH)_6$	1.33	

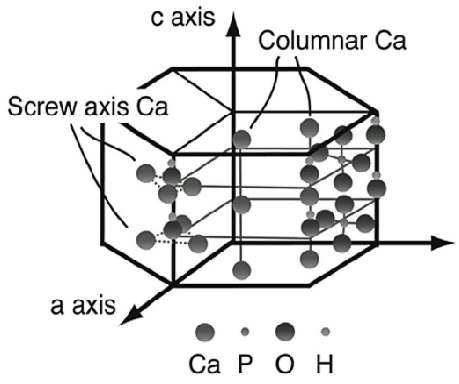

Figure 2. Crystal structure of hydroxyapatite[30]

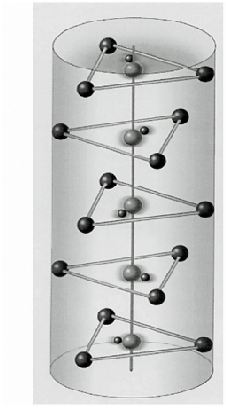

Figure 3. "Calcium-triangle" and "Calcium tunnel" in the hydroxyapatite crystal structure (original)

role of polyphosphate in the bone formation was repostulated[80]. The role of amorphous phases in mineralization of HAp in biological tissues such as bone continues to be a subject of great research interest[81].

Studies on the early phases of the calcification can be divided into two groups: those carried out up to about 1960 on the basis of histological, histochemical, biochemical and biophysical methods on topics related to the nature and composition of the inorganic component of hard tissues, and those carried out after 1960s by applying the more refined modern methods[74]. With specific reference to bone that three concepts were prominent at that time: that the bone mineral is carbonateapatite; that it is a calcium carbonate mixed with HAp; or that it is a mixture of TCP and calcium carbonate. In 1985, Posner[73] stated that "the bone

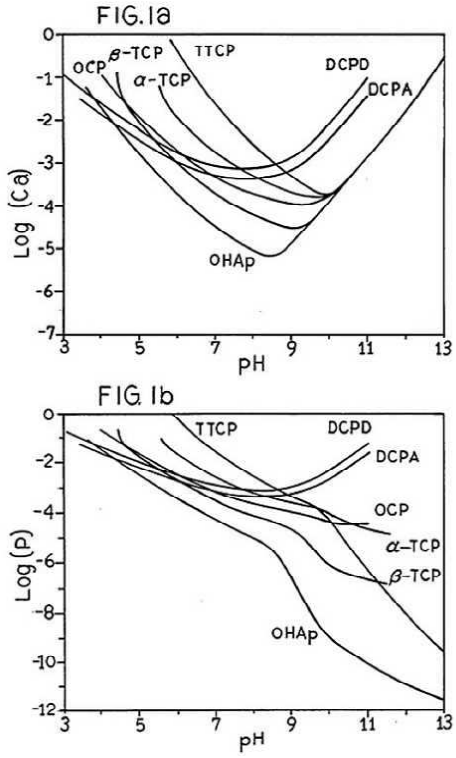

Figure 4. Stability of calcium phosphates[70)]

mineral is a calcium and hydroxyl-deficient, hydrogen and carbonate-containing analogue of HAp characterized by structural imperfection". The early stage of calcification problem still remained to be clarified.

For the more information of apatite formation in body system, refer the references[82-85)].

Biological Apatites

Nonstoichiometry of the Inorganic Composition in Hard Tissues

The word "Hard Tissue" is also used in the other vertebrate and invertebrate kingdom such as fish scale, shell of a tortoise, spicules of sand star and coral, beaks of cattle fish, shells of bivalves and Brachiopod, test of Foraminifera, and so on[3,74)]. "Hard Tissues" may not be defined clearly, but usually including tooth enamel, dentin, cementum, and bone in vertebrates and also including pathological concretions such as dental calculus, salivary stones, and many pathological calculus[34,86)]. Except otolith in the inner ear, all the inorganic parts of human bone and teeth are composed of biological apatites.

As early as 1926, the inorganic phases of bone and teeth are basically calcium HAp[9)]. The detailed crystal structure of human tooth enamel apatite was determined[46,87)]. The term "Biological Apatite" is used for these apatite which were produced by organisms. However, the minor but important differences between these biological apatites and mineral/synthetic apatites were not clarified still now. It was notable that one of the origin of life hypothesis there is "Apatite Hypothesis"[82,88)].

Limited to the tooth enamel, dentin and bone in human body, the number of analytic reports for these materials have been published. However, unexpectedly the chemical compositions for these could not be converged. For human enamel, the most hardest and highly mineralized tissue in body, Ca wt % ranged from 33.6 to 39.4, P wt % from 16.1 to 18.0, and CO_3 from 1.95 to 3.66, Ca/P ratio (by weight) from 1.92 to 2.17, Ca/P (molar) from 1.5 to 1.68[10,89)]. There arose such an idea of "nonstoichiometric apatite" or "Ca-deficient apatite" that could explain the non uniform analytical data in part. Several theories have been put forward to explain the nonstoichiometry of biological apatite, such as deficiency of calcium ions, excess ion adsorption on the crystal surface, lattice substituions, and the addition of a second phase[90-93)]. When the ionic substitutions occur in the apatite crystal structure, the values of the a- and c-axes, and the a/c ratio, may change[6,34)]. However, the high carbonate content leaded the old investigators to mistakes as these biological inorganic components might be composed of some calcium carbonates together with calcium phosphate and calcium oxide. And the investigators at that time considered that the nonstoichiometry of these inorganic matters might be due to the mixture of these components. Because, at that time, it was resumed that apatite crystal may not substitute carbonate ions so much. Then, the old anatomy and histology textbooks unfortunately described as the inorganic components being calcium phosphate plus calcium carbonate. This misunderstood was corrected later when the biological apatites are proved as carbonated apatite[53,94)]. And hereafter it has been verified that the highly carbonated apatite is the common feature for the biological apatite.

Although it had been revealed that human teeth and bones are composed of biological apatites, their chemical compositions were not unified and varied from parts to parts of bones and teeth, and among individual teeth and bones[95-100)]. The variation in the chemical composition of the biological apatites may be due to such conditions of the cell activity, timing, physiological and also circadian rhythm of these hard tissue formation. For the more information on the chemistry of hard tissues, refer the references[4,6,34,74,78,101,102)].

Biological Apatite as Carbonate Apatite

Biological apatites, occur as the inorganic portion of many hard tissues, differ from pure HA in stoichiometry, composition and crystallinity, and therefore have different physical and mechanical properties. Biological apatites are typically calcium deficient carbonated calcium HAp, so are strictly carbonate apatites rather than HAp[6,34)].

Carbonate ion substitution in the apatite crystal structure occurs in two site, namely A-site substitution for OH ion, and B-site for PO4 ion[103-105)]. FTIR spectroscopic studies of synthetic and biological carbonate apatite showed that the absorption bands at

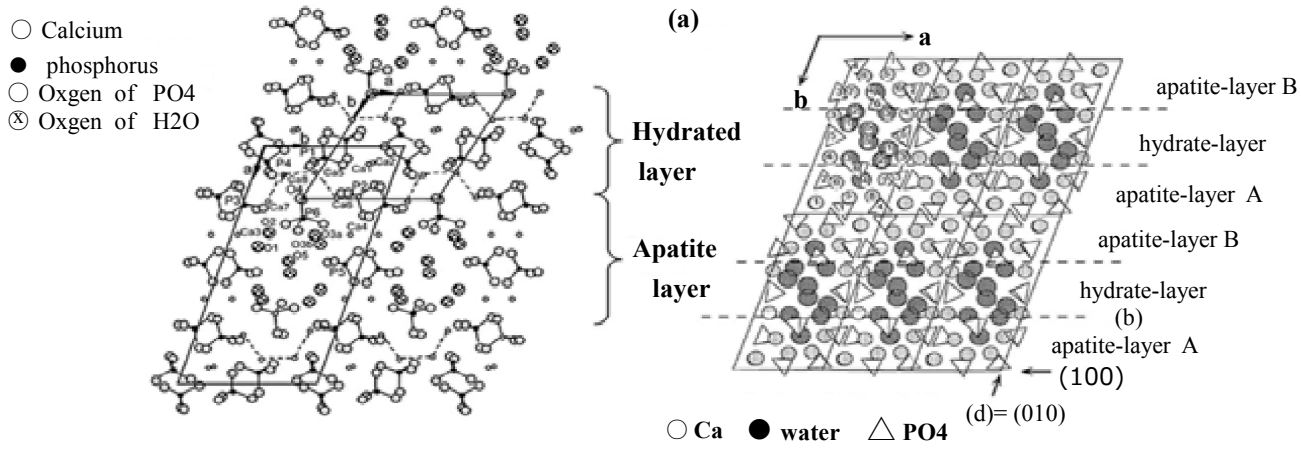

Figure 5. Relationship between the crystal structures of hydroxyapatite and octacalcium phosphate[66)]

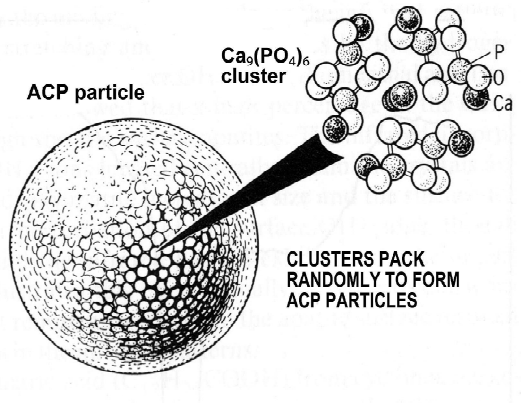

Figure 6. Structure of amorphous calcium phosphate[71)]

670 cm^{-1} and 757 cm^{-1} can be attributed to A-site carbonate, and 692 cm^{-1} and 718 cm^{-1} to B-site[106)], 878, 1465 and 1550 cm^{-1} for A-site, and 872, 1415 and 1500 cm^{-1} for B-site[107)]. The bands at PO4 v3 domain of A-site and B-site appeared at 1108 cm^{-1} and 1070 cm^{-1} , respectively[108)].

Substitution of components in these biological apatites occurs in a couple manner in order to balance the electrical charges, so-called Type B substitution[94)]. This means that there is an equivalent calcium for sodium as phosphate for carbonate modification and the other substitutions[109-111)]. As a result, biological apatites vary in the products after sintering[112)]. Thus, sintering enamel or dentin above 800 ℃ gives HA and small amounts of b-TCP varying the b-TCP/HA ratio depending on the portions or individuals[49,95,96)].

For the more information of biomineralization concerning to biological apatites, refer the references [60,61,83,113-116)].

Biomedical Application of Apatite and Calcium Phosphates

In Vitro and In Vivo Cell Reactions of Synthetic Apatites

The cell reactions with the synthetic calcium phosphates have been investigated and the cell afinity has been clarified[117,118)]. Zinc and/or magnesium containing calcium phosphate[119-123)], and the osteoconductive calcium phosphates[124-128)] have been studied and applied to clinical uses.

Calcium Phosphates as Biomedical Applications and Food Additives

Calcium phosphates and biphasic calcium phosphate ceramics can be candidate for the bone-scaffold and restorative dentistry[129-135)]. Calcium phosphate based coatings have been developed and used in clinical dentistry and medicine[136-138)].

Amorphous calcium phosphate is also the candidate for the bone tissue repair substartes as well as the precursor of biological apatite *in vivo*[73,139)]. Tetracalcium phosphate[140)], αTCP[141,142)], and OCP[143)].

Antibacterial and mineralizing calcium phosphate-based treatments are developped[144,145)], and drug delivery system using some calcium phosphates are now adopted to clinical applications[146,147)]. A new synthetic bone mineral (SBM) diet was developed and the effect was confirmed by animal experiment[148-150)].

Acknowledgements

This paper would be a part of the series of "Calcium Phosphates from Basic to Application" writing planned by Prof. Racquel Z. LeGeros together with some collaborators. However, she passed away so suddenly in 2012, the work was left. The authors promised to write with her while in life, and write down here that the work should be completed at least in part.

References

1. LeGeros RZ, Pan CM, Suga S and Watabe N. Crystallochemical properties of apatite in atremate brachiopod shells. Calcif Tissue Int 37: 98100, 1985

2. Lowenstam HA and Weiner S. On Biomineralization. Oxford, New York, 1989
3. Rohanizadeh R and LeGeros RZ. Mineral phase in linguloid brachiopod shell: Lingula adamsi. Lethaia 40: 6168, 2007
4. LeGeros RZ. Biological and Synthetic Apatites. In: Hydroxyapatite and related materials, ed by Brown PB and Constantz B, CRC, Boca Raton, 1994, pp 328.
5. Watabe N. Biomineralization Studies : Present status and Future Perspectives (in Japanese). In: Biomineralization and Hard Tissue of Marine Organisms, ed by Wada K and Kobayashi I, Tokai Univ Press, Tokyo, 1996, pp 925.
6. McConnell D. Apatite. Springer-Verlag, Wien, 1973
7. Dana JD and Brush GJ. A system of mineralogy, Descriptive mineralogy, comprising the most recent discoveries. 5th ed, John Wiley & Sons, New York, 1868
8. Nriagu JO. Phosphate Minerals: Their Properties and General Modes of Occurrence. In: Phosphate Minerals, ed by Nriagu JO and Moore PB, Springer-Verlag, Wien, 1984, pp 1136.
9. De Jong WF. La substance minerale dans les os. Tec Trav Chim 45: 445458, 1926
10. Dallemagne MJ and Richelle LJ. Inorganic chemistry of bone. In: Biological Mineralization, ed by Zipkin I, Wiley Interscience, John Wiley & Sons, New York, 1973, pp 2342.
11. Rowles SL. Chemistry of the mineral phase of dentine. In: Structural and Chemical Organization of Teeth, ed by Miles AEW, Academic Press, London, 1976, pp 201246.
12. Brudevold F and Soremark R. Chemistry of the mineral phase of enamel. In: Structural and Chemical Organization of Teeth, ed by Miles AEW, Academic Press, London, 1976, pp 247278.
13. Posner AS. The mineral of bone. Clin Orthop Relat Res 200: 8799, 1985
14. Boskey A. Amorphous calcium phosphate: The contention of bone. JDR 76; 14331436, 1997
15. Eanes ED, Termine JD and Posner AS. Amorphous calcium phosphate in skeletal tissues. Clin Orthop Relat Res 53: 223235, 1967
16. Grynpas MD, Bonar LC and Glimcher MJ. Failure to detect an amorphous calcium phosphate solid phase in bone mineral: a radial distribution function study. Calcif Tissue Int 36: 291301, 1984
17. Simkiss K. Amorphous minerals and theories of biomineralization. In: Mechanisms and Phylogeny of Mineralization in Biological Systems, ed by Suga S and Nakahara H, Springer, Tokyo, 1991, pp 375382.
18. Eanes ED. Amorphous calcium phosphate. Monogr Oral Sci 18: 130147, 2001
19. LeGeros RZ. Formation and transformation of calcium phosphates: relevance to vascular calcification. Z Kardiol 90 (S3): 116124, 2001
20. Rey C, Comb, C. Drouet C and Glimcher MJ. Bone mineral: Update on chemical composition and structure. Osteoporos Int 20: 10131021, 2009
21. Mahamid J, Addadi L and Weiner S. Crystallization pathways in bone. Cells Tissues Organs 194: 9297, 2011
22. Dorozhkin SV. Amorphous Calcium Orthophosphates: Nature, Chemistry and Biomedical Applications. Int J Mater Chem 2: 1946, 2012
23. Veis A and Dorvee JR. Biomineralization mechanisms: a new paradigm for crystal nucleation in organic matrices. Calcif Tissue Int 93: 307315, 2013
24. Very JM and Baud CA. X-ray diffraction of calcified tissues. In: Methods of Calcified Tissue Preparation, ed by Dickson GR, Elsevier, Amsterdam, 1984, pp 369390.
25. Elliott JC. Infrared and Raman spectroscopy of calcified tissues. In: Methods of Calcified Tissue Preparation, ed by Dickson GR, Elsevier, Amsterdam, 1984, pp 413434.
26. Wyckoff RWG. The microstructure and composition of fossils. In: Biological Mineralization, ed by Zipkin I, Wiley Interscience, John Wiley & Sons, New York, 1973, pp 527546.
27. Sakae T. Proboscidea fossil teeth suggest the evolution of enamel crystals. In: Mechanisms and Phylogeny of Mineralization in Biological Systems, ed by Suga S and Nakahara H, Springer, Tokyo, 1991, pp 477481.
28. Pan Y and Fleet ME. Compositions of the Apatite Group Minerals: Substitution Mechanisms and Controlling Factors. In: PHOSPHATES: Geochemical, Geobiological, and Materials Importance, ed by Kohn MJ, Rakovan J and Hughes JM, Reviews in Mineralogy and Geochemistry, vol.48, Mineralogical Society of America, Washington, DC, 2002, pp 1349.
29. Pasero M, Kampf AR, Ferraris C, Pekov IV, Rakovan J and White TJ. Nomenclature of the apatite supergroup minerals. Eur J Mineral 22: 163179, 2010
30. Boudreau AE. Fluid evolution in layered intrusions: Evidence from the chemistry of halogen bearing minerals. In: Magmas, Fluids, and Ore Deposits, ed by Thompson JFH, Mineralogical Association of Canada, Short Course Series, vol.23, 1995, pp 2545.
31. Hughes JM and Rakovan J. The crystal structure of apatite, a5(PO4)3(F,OH,Cl). In: PHOSPHATES: Geochemical, Geobiological, and Materials Importance, ed by Kohn MJ, Rakovan J and Hughes JM, Reviews in Mineralogy and Geochemistry, vol.48, Mineralogical society of America, Washington, DC, 2002, pp 112.
32. JCPDS cards (ASTM cards). PDF, Powder Diffraction File, ICDD, International Center for Diffraction Data, Newtown Square, PA, USA, 2000
33. Elliott JC, Mackie PE and Young RA. Monoclinic

hydroxyapatite. Science 180; 10551057, 1973

34. LeGeros RZ and LeGeros JP. Phosphate Minerals in Human Tissues. In: Phosphate Minerals, ed by Nriagu JO and Moore PB, Springer-Verlag, Berlin, 1984, pp 351383.
35. Trueman CN and Tuross N. Trace Elements in Recent and Fossil Bone Apatite. In: PHOSPHATES: Geochemical, Geobiological, and Materials Importance. ed. by Kohn MJ, Rakovan J and Hughes JM, Reviews in Mineralogy and Geochemistry, vol.48, Mineralogical Society of America, Washington, USA, 2002, pp 489521.
36. Gleadow AJW, Belton DX, Kohn BP and Brown RW. Fission track dating of phosphate minerals and the thermochronology of apatite. In: PHOSPHATES: Geochemical, Geobiological, and Materials Importance, ed by Kohn MJ, Rakovan J and Hughes JM, Reviews in Mineralogy and Geochemistry, vol.48, Mineralogical Society of America, Washington, DC, USA, 2002, pp 579630.
37. Nasdala L, Gotze J, Hanchar JM, Gaft M and Krebetschek R. Luminescence techniques in Earth sciences. In: Spectroscopic Methods in Mineralogy, ed by Beran A and Libowitzky E, European Mineralogical Union Notes in Mineralogy, vol.6, Eç•tvç•s University Press, Budapest, 2004, pp 4391.
38. Carlson D. X-ray crystallographic studies on apatites and calcified tissues. Acta Radiol. Suppl 121, 1955
39. Bale WF, Hodge HC and Warren SL. Roentgenray diffraction studies of enamel and dentin. Am J Roentgenol Radium 32: 369376, 1934
40. Trautz OR. X-ray diffraction of biological and synthetic apatites. Annals NY Academy of Sci 60: 697712, 1955
41. NáraySzabó, S. The structure of apatite (CaF) Ca4 (PO4) 3. Z. Kristallogr 75: 387398, 1930
42. Mehmel M. Uber die Struktur des Apatits. IZ Kristallogr 75: 323331, 1930
43. Posner AS, Stutman JM and Lippincott ER. Hydrogen bonding in calcium deficient hydroxyapatite. Nature 188: 486487, 1960
44. Kay MI, Young RA and Posner AS. Crystal structure of hydroxyapatite. Nature 204: 10501053, 1964
45. Sudarsanan K and Young RA. Significant precision in crystal structure details: Holly Springs hydroxyapatite. Acta Crystallographica B25: 15341543, 1969
46. Young RA and Mackie PE. Crystallography of human tooth enamel: initial structure refinement. Materials Res Bull 15: 1729, 1980
47. Young RA. Implications of atomic substitutions and other structural details in apatites, J Dent Res 53: 193203, 1974
48. Elliott JC. Structure and Chemistry of the Apatites and Other Calcium Orthophosphates. Elsevier, Amsterdam, 1990.
49. LeGeros RZ. Calcium Phosphates in Oral Biology and Medicine. Karger, Basel, 1991.
50. Elliott JC, Wilson RM and Dowker SEP. Apatite Structures. Advances in Xray Analysis 45: 172181, 2002
51. Dorozhkin SV. Calcium Orthophosphates: Applications in Nature, Biology, and Medicine. CRC, London, 2012.
52. Hughes JM, Nekvasil H, Utsunisik G, Lindsley DH, Coraor AE, Vaughn J, Phillips BL, McCubbin FM and Woerner WR. Solid solution in the flourapatite chlorapatite binary system: Highprecision crystal structure refinements of synthetic FCl apatite. Amer Miner 99: 369376, 2014
53. LeGeros RZ, LeGeros JP, Trautz OR and Klein E. Spectral properties of carbonate in carbonate containing apatites. Dev Appl Spectrosc 7B: 312, 1970
54. Schmidt WJ and Keil A. Polarizing Microscopy of Dental Tissues. Pergamon Press, Oxford, 1971.
55. Dickson GR. Methods of Calcified Tissue Preparation, Elsevier, Amsterdam, 1984.
56. Urlich L. Archaeometry. VCH, Weinheim, 1987.
57. Beran A and Libowitzky E. Spectroscopic Methods in Mineralogy. European Mineralogical Union, EMU, Note in Mineralogy, vol. 6, Eç•tvç•s University Press, Budapest, 2004.
58. Epple M. Modern methods of investigation in biomineralization. In: Biomineralization: Progress in Biology, Molecular Biology and Application, 2nd ed, ed by Baeuerlein E, Wiley VCH, Weinheim, 2004, pp 307325.
59. Lasch P and Kneipp J. Biomedical Vibrational Spectroscopy. WileyInterscience, John Wiley & Sons, New York, 2008
60. Bazin D, Chappard C, Combes C, Carpentier X, Rouziere S, Andre G, Matzen G, Allix M, Thiaudiere D, Reguer S, Jungers P and Daudon M. Diffraction techniques and vibrational spectroscopy opportunities to characterize bones. Osteoporosis Int, 20: 10651075, 2009
61. Yoreo JD. Research Methods in Biomineralization Science. Academic Press, Elsevier, San Diego, 2013.
62. DiMasi E and Gower LB. Biomineralization Sourcebook: Characterization of Biominerals and Biomimetic Materials. CRC, London, 2014.
63. Corbridge DEC. Phosphorus, An outline of its chemistry, biochemistry and technology. Elsevier, Amsterdam, 1985. Averbuch Pouchot MT and Durif A. Topics in Phosphate Chemistry. World Science, Singapore, 1996.
64. Elliott JC. Calcium phosphate biominerals, In: PHOSPHATES: Geochemical, Geobiological, and Materials Importance.,ed. by Kohn MJ, Rakovan J and Hughes JM, Reviews in Mineralogy and Geochemistry, vol.48, Mineralogical Society of America, Washington, DC, 2002, pp 427453.
65. Nancollas GH. The Nucleation and Growth of Phosphate Minerals. In: Phosphate Minerals, ed by Nriagu JO and

Moore PB, Springer-Verlag, Berlin, 1984, pp 137170.
66. Brown WE. Octacalcium phosphate and hydroxyapatite: Crystal structure of octacalcium phosphate. Nature 196: 1048, 1962.
67. Brown WE, Smith JP, Lehr JR and Frazier AW. Octacalcium Phosphate and Hydroxyapatite: Crystallographic and chemical relations between octacalcium phosphate and hydroxyapatite. Nature 196: 10501055, 1962
68. Landis WJ. An overview of vertebrate mineralization with emphasis on collagen-mineral interaction. Gravit Space Biol Bull 12: 1526, 1999
69. Suzuki K, Sakae T and Koxawa Y. Helix structure of ribbon-like crystals in bovine enamel. Connect Tissue Res 38: 113117, 1998
70. Chow LC and Eanes ED. Octacalcium Phosphates. Karger Medical and Scientific Pub, Basel, 2001
71. Eanes ED, Gillessen IH and Posner AS. Intermediate states in the precipitation of hydroxyapatite. Nature 208: 365367, 1965
72. Wuthier RE, Rice GS, Wallace JEB, Weaver RL, LeGeros RZ and Eanes ED. In vitro precipitation of calcium phosphate under intracellular conditions: Formation of brushite from an amorphous precursor in the absence of ATP. Calcif Tissue Int 37: 401410, 1985
73. Posner AS. The mineral of bone. Clin Orthop Relat Res 200: 8799, 1985
74. Bonucci E. Biological Calcification. Springer Science & Business Media, Berlin, 2007
75. Christ C and Rey C. Amorphous calcium phosphates: synthesis, properties and uses in biomaterials. Acta Biomater 6: 33623378, 2010
76. Dorozhkin SV. Amorphous Calcium Orthophosphates: Nature, Chemistry and Biomedical Applications. Intl J Mater Chem 2: 1946, 2012
77. Glimcher MJ. Bone: Nature of the calcium phosphate crystals and cellular, structural, and physical chemical mechanisms in their formation. In: Medical Mineralogy and Geochemistry. Reviews in Mineralogy and Geochemistry, vol.64, ed by Sahai N and Schoonen MAA, Mineralogical Society of America, Washington, DC, 2006, pp 223282.
78. Boskey AL. Mineralization of Bones and Teeth. Elements, 3: 387393, 2007
79. Colfen H. Biomineralization: A crystal clear view. Nature Mater 9: 960961, 2010
80. Omelon S, Georgiou J, Hennemen ZJ, Wise LM, Sukhu B, Hunt T, Wynnckyj C, Holmyard D, Bielecki R and Grynpas MD. Control of vertebrate skeletal mineralization by polyphosphates. PLoS ONE, 4: e5634, 2009
81. Driessense FCM and Verbeeck RMH. Biominerals. CRC, London, 1990.
82. Newman WF and Newman MW. In the Beginning There Was Apatite. In: Biological Mineralization, ed by Zipkin I, John Wiley & Sons, New York, 1973, pp 319.
83. Mann S. Mineralization in biological system. In: Inorganic Elements in Biochemistry, Structure and Bonding vol. 54, ed by Connett PH, Follmann H, Lammers M, Mann S, Odom JD and Wetterhahn KE, Springer, Berlin, 1983, pp 125174.
84. Weiner S. Organization of Extracellularly Mineralized Tissues: A Comparative Study of Biological Crystal Growth. CRC Critical Reviews in Biochemistry and Molecular Biology, 20: 365408, 1986
85. Pasteris JD, Wopenka B and Valsami-Jones E. Bone and tooth mineralization: Why apatite? Elements 4: 97104, 2008
86. LeGeros RZ. Magnesium in normal and pathological calcifications. In: Mechanisms and Phylogeny of Mineralization in Biological Systems, ed. by Suga S and Nakahara H, Springer, Tokyo, 1991, pp 315319.
87. Wilson RM, Elliott JC and Dowker SEP. Rietveld refinement of the crystallographic structure of human dental apatites. Am Mineralogist 84: 14061414, 1999
88. Palazzo B, Walsh D, Iafisco M, Foresti E, Bertinetti L, Martra G, Bianchi CL, Cappelletti G and Roveri N. Amino acid synergetic effect on structure, morphology and surface properties of biomimetic apatite nanocrystals. Acta Biomaterialia 5: 12411252, 2009
89. Williams RAD and Elliott JC. Basic and Applied Dental Biochemistry. Churchill Livingstone, Longman, Edinburgh, 1979.
90. Newman WD and Neuman MW. The nature of the mineral phase of bone. Chem Rev 53: 145, 1953
91. Posner AS and Duyckaerts G. Infrared study of the carbonate in bone, teeth and francolite. Experientia 10: 424425, 1954
92. Eanes ED and Posner AS. A note on the crystal growth of hydroxyapatite precipitated from aqueous solutions. Mater Res Bull 5: 377383, 1970
93. Wu WJ and Nancollas GH. Factors controlling crystallization of calcium phosphates on solid surfaces. In: Bioceramics 11, ed by LeGeros RZ and LeGeros JP, World Science, Singapore, 1998, pp 469472.
94. Zapanta-LeGeros R. Effect of carbonate on the lattice parameters of apatite. Nature 206: 403404, 1965
95. Sakae T. Xray diffraction and thermal studies of crystals from the outer and inner layers of human dental enamel. Arch oral Biol 33: 707713, 1988
96. LeGeros RZ, Sakae T, Bautista C, Retino M and LeGeros JP. Magnesium and Carbonate in Enamel and Synthetic Apatites. Amer Dent Res 10: 225231, 1996
97. Suwa T, Sakae T, Nakada H, LeGeros RZ and Kobayashi K. Variation in composition of bone surrounding implants. Key Engin Mater 309311: 1922, 2006

98. Numata Y, Nakada H, Sakae T, Kimura-Suda H, LeGeros Z, Kobayashi K and Makimura M. Qualitative study of the New Bone formation Surrounding the Ti-implant by FTIR and Polarizing Microscope. J Hard Tissue Biol 17: 131140, 2008
99. Nakada H, Sakae T, Tanimoto Y, Teranishi M, Kato T, Watanabe T, Saeki H, Kawai Y and Legeros RZ. Assessment of the Quality of Newly Formed Bone around TitaniumAlloy Implants by Using X-Ray Photoelectron Spectroscopy. Int J Biomater 2012: 615018, 1-17, 2012
100. Sakae T, Nakada H, Teranishi M, Kato T, Suzuki S, Yanagawa A, Yasuda N, Ochiai S, Kitagawa N, Kawai Y and LeGeros RZ. Comparison between the lateral and medial femur in low-mineral-diet fed overi-ectomized rats using Raman spectral analysis. Key Engen Mater 529530: 337340, 2012
101. Elliott JC. The problems of the composition and structure of the mineral components of the hard tissues. Clin Orthop Rel Res 93: 313345, 1973
102. LeGeros RZ and Ben-Nissan B. Introduction to Synthetic and Biologic Apatites. In: Advances in Calcium Phosphate Biomaterials, ed by Ben-Nissan B, Springer Series in Biomaterials Science and Engineering, Berlin, 2014, pp 119.
103. LeGeros RZ, Trautz OR, Klein E and LeGeros JP. Two types of carbonate substitution in the apatite structure. Experientia 25: 57, 1969
104. Rey C, Collins B, Goehl T, Dickson IR and Glimcher MJ. The carbonate environment in bone mineral: A resolution-enhanced fourier transform infrared spectroscopy study. Calcif Tissue Int 45: 157164, 1989
105. Fleet ME. The carbonate ion in hydroxyapatite: Recent X-ray and infrared results. Front Biosci E5: 643652, 2013
106. Feki H El, Rey C and Vignoles M. Carbonate ions in apatites: Infrared investigations in the v4 CO3 domain. Calcified Tissue Int 49: 269274, 1991
107. Elliott JC, Holcomb DW and Young RA. Infrared determination of the degree of substitution of hydroxyl by carbonate ions in human dental enamel. Calcif Tissue Int 37: 372375, 1985
108. Penel G, Leroy G, Rey C and Bres E. Micro-Raman Spectral Study of the PO4 and CO3 Vibrational Modes in Synthetic and Biological Apatites. Calcif Tissue Int 63: 475481, 1998
109. McConnell D, Termine JD and Posner AS. Infrared absorption of carbonate apatite. Science 155: 607608, 1967
110. LeGeros RZ, Trautz OR, LeGeros JP, Klein E and Shirra WP. Apatite crystallites: effect of carbonate on morphology. Science 155: 14091411, 1967
111. LeGeros RZ, Trautz OR, LeGeros JP and Klein E. Carbonate substitution in the apatite structure. I. Bull Soc Chim Fr, Special No., 17121718, 1968
112. Holcomb DW and Young RA. Thermal decomposition of human tooth enamel. Calcif Tissue Int 31: 189201, 1980
113. Wopenka B and Pasteris JD. A mineralogical perspective on the apatite in bone. Materi Scie Engin C 25: 131143, 2005
114. Mueller WEG. Molecular Biomineralization: Aquatic Organisms Forming Extraordinary Materials (Progress in Molecular and Subcellular Biology / Marine Molecular Biotechnology), Springer, Berlin, 2011
115. Bonucci E. The Mineralization of Bone and Its Analogies with Other Hard Tissues. In: Advanced Topics in Crystal Growth, ed by Ferreira SO, INTECH, Open Science, 2013.
116. Kaim W, Schwederski B and Klein A. Bioinorganic Chemistry Inorganic Elements in the Chemistry of Life: An Introduction and Guide (Inorganic Chemistry: A Textbook Series), John Wiley & Sons, UK, 2013
117. LeGeros RZ and LeGeros JP. DENSE HYDROXYAPATITE. In: An Introduction to Bioceramics, ed by Hench LL and Wilson J, World Science, Singapore, 1993, pp. 139180.
118. MacMillan AK, Lamberti FV, Moulton JN, Geilich BM and Webster TJ. Similar healthy osteoclast and osteoblast activity on nanocrystalline hydroxyapatite and nanoparticles of tricalcium phosphate compared to natural bone. Int J Nanomed 9: 562737, 2014
119. Cheng PT, Grabher JJ and LeGeros RZ. Effects of magnesium on calcium phosphate formation. Magnesium 7: 123132, 1988
120. Okazaki M and LeGeros RZ. Properties of heterogeneous apatites containing magnesium, fluoride, and carbonate. Adv Dent Res 10: 252259, 1996
121. LeGeros RZ, Bleiwas CB, Retino M and LeGeros JP. Zinc effect on the in vitro formation of calcium phosphates: relevance to clinical inhibition of calculus formation. Am J Dent 12: 6570, 1999
122. Yamada Y, Ito A, Kohjima H, Sakane M, Miyaka S, Uemura T and LeGeros RZ. Inhibitory effect of Zn2+ in zinc-containing beta-tricalcium phosphate on resorbing activity of mature osteoclasts. J Biomed Mater Res 84A: 344352. 2008
123. Li X, Sogo Y, Ito A, Mutsuzaki H, Ochiai N, Kobayashi T, Nakamura S, Yamashita K and Legeros RZ. The optimum zinc content in set calcium phosphate cement for promoting bone formation *in vivo*. Mater Sci Eng C Mater Biol 29: 969975, 2009
124. LeGeros RZ. Biodegradation and bioresorption of calcium phosphate ceramics. Clinical Materials 14: 6588, 1993
125. LeGeros RZ, Kijkowska R, Bautista C and LeGeros JP. Synergistic effects of magnesium and carbonate on properties of biological and synthetic apatites. Connect Tissue Res 33: 2039, 1995
126. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. Clin Orthop 8198, 2002
127. LeGeros RZ. Calcium phosphate-based osteoinductive

materials. Chem Rev 108: 474253, 2008

128. Dorozhkin SV. Medical application of calcium orthophosphate bioceramics. BIO 1: 151, 2011
129. LeGeros RZ, Chohyeb A and Shulman A. Apatitic calcium phosphate: possible dental restorative materials. J Dent Res 61: 343, 1982
130. Jean A, Kerebel B, Kerebel LM, LeGeros RZ and Hamel H. Effects of various calcium phosphate biomaterials on reparative dentine bridge formation. J Endod 14: 8387, 1988
131. LeGeros RZ, LeGeros JP, Daculsi G and Kijkowska R. Calcium phosphate biomaterials: preparation, properties and biodegradation. In: Encyclopedia Handbook of Biomaterials and Bioengineering, vol.2, ed by Wise DL, Tarantalo DJ, Altobelli DE, Yaszemski MJ, Gresser JD and Schwartz ER, Marcel Dekker, New York, 1995, pp 14291463.
132. LeGeros RZ, Lin S, Rohanizadeh R, Mijares D and LeGeros JP. Biphasic calcium phosphate bioceramics: preparation, properties and applications. J Mater Sci Mater Med 14: 201209, 2003
133. Daculsi G and LeGeros RZ. Tricalcium phosphate/ hydroxyapatite biphasic ceramics. In: Bioceramics and their clinical applications, ed by Kokubo T, Woodhead Pub, Elsevier, Amsterdam, 2008, pp 395423.
134. Garrido CA, Lobo SE, Turíbio FM and Legeros RZ. Biphasic calcium phosphate bioceramics for orthopaedic reconstructions: clinical outcomes. Int J Biomater 2011: 129727, 2011
135. Iafisco M and Delgado-Lopez JM. Apatite: Synthesis, Structural Characterization and Biomedical Applications. Nova Sci Pub, New York, 2014.
136. LeGeros JP, LeGeros RZ, Burgess A, Edwards B and Zitelli J. X-ray diffraction method for the quantitative characterization of calcium phosphate coatings. In: Characterization and Performance of Calcium Phosphate Coatings for Implants, ed by Horowiz E and Parr JE, ASTM STP 1196. American Society for Testing Materials, Philadelphia, 1994, pp 3342.
137. Rohanizadeh R, LeGeros RZ, Harsono M and Benavid A. Adherent apatite coating on titanium substrate using chemical deposition. J Biomed Mater Res 72A:428438, 2005
138. Zavgorodniy AV, Mason RS, LeGeros RZ and Rohanizadeh R. Adhesion of chemically deposited monetite coating to a Ti substrate. Surface Coat Technol 206: 44334438, 2012
139. Julien M, Khairoun I, LeGeros RZ, Delplace S, Pilet P, Weiss P, Daculsi G, Bouler JM and Guicheux J. Physicochemical-mechanical and *in vitro* biological properties of calcium phosphate cements with doped amorphous calcium phosphates. Biomaterials 28; 95665, 2006
140. Moseke C and Gburek U. Tetracalcium phosphate: Synthesis, properties and biomedical applications. Acta Biomater 6: 381523, 2010
141. Wakae H, Takeuchji A, Udoh K, Matsuya S, Munar M, LeGeros RZ, Nakagawa M, Nakashima A and Ishikawa K. Fabrication of cancellous bone type carbonate apatite foam by hydrothermal conversion of alpha-tricalcium phosphate in carbonate solutions. J Biomed Mater Res 87A: 957963. 2008
142. Carrodeguas RG and De Aza S. áTricalcium phosphate: synthesis, properties and biomedical applications. Acta Biomater 7: 353646., 2011
143. Lin S, LeGeros RZ and LeGeros JP. Adherent octacalcium phosphate coating on titanium alloy using a modulated electrochemical deposition method. J Biomed Mater Res 66A: 810828, 2003
144. Ito A, Senda K, Sogo Y, Oyane A and LeGeros RZ. Dissolution of zinc-containing tricalcium phosphate ceramics. Biomed Mater 1:134138, 2006
145. Chou AH, LeGeros RZ, Chen Z and Li Y. Antibacterial effect of zinc phosphate mineralized guided bone regeneration membranes. Implant Dent 16: 89100, 2007
146. Daculsi G, Gauthier O, Guicheux J, Bouler JM and Aguado E. Macroporous biphasic calcium phosphate ceramics, a carrier for human growth hormone. In: Bioceramics 11, ed by LeGeros RZ and LeGeros JP, World Science, Singapore, 1998, pp 525528.
147. Nagatsuka H, Inoue M, Ishiwari Y, Tsujigiwa H, Huang B, Nagai N and LeGeros RZ. Bone augmentation by BMP-collagen I and BMP-porous block hydroxyapatite composite in rat calvarial subperiosteum. In: Bioceramics 11, ed by LeGeros RZ and LeGeros JP, World Science, Singapore, 1998, pp 549552.
148. LeGeros RZ, Mijares D, Yao F, Tannous S, Catig G, Xi Q, Dias R and LeGeros JP. Synthetic bone mineral (SBM) for osteoporosis therapy: Part I. Prevention of bone loss from mineral deficiency. Key Engineer Mater 361363, 4346. 2007
149. Mijares D, Kulkarni A, Lewis K, Yao F, Xi Q, Tannous S, Dias R and LeGeros RZ. Oral bone loss induced by mineral deficiency in a rat model: effect of a synthetic bone mineral (SBM) preparation. Arch Oral Biol 57: 126473, 2012
150. Nakada H, Watanabe T, Takahashi T, Fujita K, Tanimoto Y, Teranishi M, Kato T, Kawai Y, Sakae T and LeGeros RZ. A New Synthetic Diet Increased Bone Mineral Density and Strength of Ovariectomized Rat. Bioceram Dev Appl S1: 003, 2013