

Long-term results of the Coralline Porous Hydroxyapatite HAP-200 as bone implant's biomaterial in Orthopedics and Traumatology

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RESUMEN. Se estudió una muestra de 486 pacientes implantados con Hidroxiapatita Porosa Coralina HAP-200, con un periodo de evolución de 1 a 6 años. El trabajo se realizó en cuatro hospitales, tres de Cuba y uno de México, siguiendo un protocolo conjunto de investigación que permitió unificar los criterios de inclusión, la indicación del tratamiento, los procedimientos quirúrgicos y el seguimiento y observación en el postoperatorio. Se estableció una clasificación por grados de I a III para la evaluación del dolor, la inflamación, la exposición del material, el edema y la sepsis, así como también, se tuvo en cuenta el aspecto radiográfico de los implantes y el estado hematológico general. En correspondencia con estos indicadores se asignó también una categorización al resultado cualitativo final tomando en consideración además, la restauración funcional lograda. Del total de pacientes, en el 26 % fue considerado excelente el resultado final logrado, el 63 % fue bueno, 7 % regular y el 4 % obtuvo la categoría de mal. Por medio de los estudios radiográficos longitudinales, se observó que al transcurrir el tiempo, el biomaterial implantado comenzó a difundirse y a disminuir su densidad con tendencia a igualarse a la del tejido óseo circundante, con la pérdida de las fronteras entre el tejido y el implante. Se apreció también un efecto osteogénico inducido y remodelación de la estructura ósea en zonas alejadas del sitio de implantación. La duración de este proceso depende entre otros factores de la edad del paciente y del tipo y magnitud de la lesión, lo cual puede ser interpretado como la asimilación del biomaterial y su incorporación a la dinámica natural del metabolismo óseo.

ABSTRACT. A sample of 486 patients implanted with Porous Coralline Hydroxyapatite HAP-200 as a bone graft substitute was studied. The period of evolution was from 1 to 6 years. A protocol of clinical investigation was followed in four orthopedic hospitals (three in Cuba and one in Mexico). It allowed standardizing the inclusion approaches, indication of the treatments, surgical procedures, as well as the postoperative evaluation. The pain, inflammation, exhibition of the material, edema and sepsis in the postoperative period was evaluated according to a degree classification from I to III as well as the radiographic aspect of the implants and the general hematological state. According to these indicators a categorization of the general final result was also established keeping in mind the achieved functional restoration. From all of the patients, 26 % was considered excellent in the achieved result, 63 % was good, 7 % fair and 4 % poor. The complications were minimum and in no case it was associated in a directly way with the implant biomaterial. By means of longitudinal radiographic studies it was observed that at the time, the implanted biomaterial begins to spread and to standardize its density with the surrounding bone environment, with the gradual loss of the tissue-implants frontiers. It is also noticed an induced osteogenic effect and remodeling of the bone structure in areas far from the implanted site. The time of duration of this process depends among other factors on the patient's age and on the type, place and magnitude of the lesion, what can be interpreted as the assimilation of the biomaterial and its incorporation to the natural dynamics of the bone metabolism.

INTRODUCTION

The Porous Coralline Hydroxyapatite HAP-200 is a biomaterial for bone implants obtained from sea corals. It has a three-dimensionally interconnected porous structure and similar chemical composition to that of the inorganic support of the bone.^{1,2} In the preclinical and clinical studies in different medical specialties has been proved their excellent biocompatibility and capacity to regenerate the damaged or lost bone tissue.³⁻⁶ Such results are in agreement with the international experience. From the point of view of the biocompatibility, tolerance to the human body and effectiveness in the cure, the hydroxyapatites are probably the best biomaterials in this field. At present there are different approaches about their osteoconductor, osteoinductor character or both as well as their biodegradation properties.^{7,8} It is predominant the tendency to classify the hydroxyapatites in general as osteoconductors and non-reabsorbables. The clinical use of these compounds in the last 20 years has confirmed its effectiveness and security as a bone graft substitute. However, most of the preclinical and clinical studies comprise relatively short periods of time and it has not been studied enough the bioactivity and biodegradation through its long-term clinical behavior. In particular, the rate of reabsorption of

different types of commercial hydroxyapatites varies considerably according to the experience of several authors.^{9,10} Apparently these characteristics are closely related to the place, type and magnitude of the treated bone lesion and its also depend on the nature of the own biomaterial, such as the chemical composition, its structures, surface activity, morphology, cristallinity, and others.

In this work the authors present their experience and the main results obtained in 6 years of study of the clinical behavior of the porous coralline hydroxyapatite HAP-200 as bone implant material in the orthopedic and traumatology specialty.

MATERIALS AND METHODS

The study shows the results obtained in the clinical evaluation of 486 patients with ages between 16 and 70 years old that presented lesions with loss of bone substance in the long bones and upper and lower limbs. All patients were operated on in four hospitals (three in Cuba and one in Mexico) following an unified investigation protocol.

The indication of the treatment was carried out according to the established norms for the clinical use of this product. The treated lesions were acquired pseudoarthrosis, postraumatic bone defects, tumorous and cystic cavities without infectious process in patients that didn't present systemic, immunologic or metabolic illnesses. All patients accepted to participate on a voluntary basis in the study.

In all of the cases the application of the biomaterial was carried out following the established surgical procedures for each case, trying to carry out a perfect curettage of the place to implant and that the biomaterial was in intimate contact with the healthy bone.

The used biomaterial was porous coralline hydroxyapatite HAP-200 in form of granules with half size from 2 to 2.5 mm for the filling of cavities and blocks preformed with different dimensions for the restoration of limited segments of bone.

The evaluation in the postoperative one was carried out by means of observation of the surgical place, adopting a classification system for degrees (I at III) for the pain, edema, sepsis and exposure of the material in the first 6 months. The hematological analysis included complete hemogram with differential, eritro-

sedimentation, and determination of calcium, phosphorous and alkaline phosphatase. The radiographic studies were carried out in the preoperative, the postoperative immediate one and then at the 7, 15, 30, 180, 360 d and finally annual during the whole time of study. It was also evaluated in a qualitative way the mobility and stability of the affected area as well as the achieved functional restoration.

Keeping in mind these parameters a classification of the final result achieved was excellent, good, fair and poor according to the main answer approaches (Table 1).

RESULTS

The postoperative clinical evaluation was followed for a period from 1 to 6 years (Table 2) at 486 implanted patients, 304 male and 182 female, with ages between 16 and 70 years (average of 37 years). The diagnoses were 160 pseudoarthrosis, 184 tumors and cysts, 26 fresh defects by fractures, 66 postraumatic segmentary defects. In 50 patients other lesions were present, among those sequels of previous osteotomy that produced reduction of extremities or other defects, located in different places (Table 3).

In relation to the inflammation of the surgical wound it was not relevant taking into account what was expected for a surgery. The edema was increased in the first days of the postoperative one and in most of the cases it diminished gradually. Ninety days later only 18 % presented slight edema and in the rest it was null. The pain was evaluated as minimum (degree I) in 65 % of the patients in the immediate postopera-

tive period and in most cases it was associated with the surgical trauma, 14 % referred slight pain (degree II) and after 90 d only 12 % had minimum pain. In general the pain was as expected for a surgery. The infec-

Table 2. Postoperative time of evolution of implanted patients.

Time of evaluation (months)	Patients
12	149
18	108
24	37
36	74
48	63
60	28
72	26
TOTAL	486

Table 3. Implanted patients and place of the lesions.

Places	Patients
Clavicle	18
Humerus	68
Radio	115
Ulna	21
Hand	11
Spine	8
Pelvis	21
Femur-hip	58
Tibia	126
Calcaneus-foot	16
Others	24
TOTAL	486

Table 1. Answer approaches considered for the general evaluation of the reached final result.

Syntoms	Answer approaches			
	Excelent	Good	Fair	Poor
Evaluation of the final result*				
Pain	0	I	II	III
Inflammation	0	I	II	III
Exposure of the material	0	I	II	III
Radiographic aspect	O+	O+	O	O, O-
Edema	0	I	II	III
Sepsis	No	No	No	Yes
Deviations of the hematologic state	Normal	I	II	III

(0) Is absent, (I) slight, (II) moderate, (III) intense. Radiographic aspect- (O+) Osseointegration, (O) non-appreciable, (O-) No osseointegration.

* A superior classifications in the evaluation of the pain, inflammation, exposure of the material, radiographic aspect and the hematological state determine the location of the final result in the lower immediate category.

tions in the immediate or late post-operative stage were presented in 9 patients, three of those evolved satisfactorily after the corresponding antibiogram and specific treatment, the rest (six) were considered as complications (Table 4).

The hematological analysis didn't show significant alterations of the hemoglobin. The sedimentation rate and the alkaline phosphatase were increased significantly in the first three months (above the normal values) reaching the maximum around 30 d after surgery.

The exposure or expulsion of the biomaterial was minimum, fundamentally exposure of isolated particles, associated with incorrect location or negligence in the surgical act and in no case it was a direct cause of complication.

In the longitudinal radiographic studies it was observed in a qualitative way a perfect osseointegration of the hydroxyapatite HAP-200. It can be seen by the increase of the density in the interface bone-implants in the first weeks and for the appearance of bone bridges among the implants and the surrounding bone tissue starting after 10 weeks. The consolidation evidences can be observed earlier in areas with a bigger component of cancellous bone, for example in the case of tumor and cystic cavities.

In general the cure was obtained in 96 % of the tried cases, with excellent results in 127 patients (26 %), they were evaluated as good in 306 (63 %) and 34 (7 %) was fair.

The cases considered as failures were 19 (4 %) which were evaluated as poor in the achieved final result. In most of them (16) it was necessary a second operation to retire the osteosynthesis or to carry out other corrections such as surgical revision by recidive of the initial lesions, but in none of them it was due to the implant material (Table 4).

DISCUSSION

The use of the different types of bone graft has been for a lot of time of great use in the orthopedic surgery. The high incidence of complications that are presented for its obtainment, nuisances and additional surgical risks for the patient in the case of the autologous and variable effectiveness due to possible rejections, non osteointegration, infections and dangers of transmission of illnesses and live virus in the heterologous, among others, are obstacles for its use in an extensive way.

Table 4. Main observed complications in the study.

Complications	Patients	(%)
Development of new pseudoarthrosis	5	1,1
Postoperative or late infection	6	1,2
Relapse in the cases of tumors	2	0,4
Second operation for faulty stability (unstable osteosynthesis)	3	0,6
Other causes (two uncertain)	3	0,6
TOTAL	19	3,9

In this study it has been demonstrated the excellent qualities of the porous coralline hydroxyapatite HAP-200 as a bone graft substitute, due to its high biocompatibility and capacity of regenerating the live tissue in the treatment of different lesions of traumatic and tumoral origin. Many of these lesions are of difficult solution and they have failed to other treatments, not being in any case complications added to the pathology.

Most of the clinical symptoms observed in the immediate postoperative stage have been inside the characteristic limits of a surgery. The increased levels of the alkaline fosfatase in the first three months could indicate in an indirect way the increase of the osteogenesis as a consequence of the acceleration of the osteoblastic activity induced by the osteoactivity of the implanted biomaterial.

The coralline hydroxyapatite HAP-200 presents a great chemical and morphological identity with the mineral support of the bone, with uniform and three-dimensionally interconnected pores with an average size of 194 nm and a microporosity from 5 to 30 nm conforming the walls. These properties facilitate the penetrating proliferation of the neoformed bone tissue into the implants and in the contact surface between the bone and the biomaterial. At the same time this phenomena contribute to the vascularization and osseointegration processes. This fact explains the radiographic observation of consolidation and osseointegration starting from the 10 weeks as an average in the implanted patients.

In general the bioactivity of the hydroxyapatites has been related to its mainly osteoconductor character, since they don't promote the bone formation in soft tissue (there is no osteoinduction).^{11,12} However, in this study was observed that the implants of the coralline hydroxyapatite HAP-200 into the bone, besides

working as a support for the growth of the new bone (osteoconduction), it promotes the formation and bone tissue remodeling in areas far from the implant. The figure 1 shows the radiography of one of the patients in this series, who suffered exposed fracture of the right humerus in its half third with distal. This case was previously operated on in several occasions (six) to apply different treatments (surgical cleaning, badge placement, screws, external fixators, implant of autologous bone, plaster, etc.). All of them were fruitless and left as additional sequel the loss of bone support including the cortical one in the whole extension of the limb. Under these conditions it was included in this study. There was applied osteosynthesis with wide badge of dynamic compression and due to the little space in the distal end the stabilization was completed with modular external fixators and complement of coralline HAP-200 to fill the bone defect. The fixators were withdrawn after 12 weeks and the radiographic control after six months reveals complete consolidation of the pseudoarthrotic focus. It is also observed clearly the regeneration process and remodeling of the bone in all the injured bone, including the filling with neoformed bone tissue of the hole that was in the upper part as a sequel of a nail in the previous treatments. After six months it was observed the complete arches of mobility of the injured limb.

The starting of biodegradation phenomena of the implanted porous coralline hydroxyapatite HAP-200 begins to be radiographically appreciated two years after surgery as an average. The process begins early with the formation of bone bridges in the frontier bone-biomaterial by formation of interfacial chemical bonds that begins to standardize the density in the contact area, making the limits between both materials disappear gradually. Then it is observed the gradual decrease of the

radiographic density of the implant until a homogeneous mass is formed with similar characteristics to the surrounding bone environment.

The behavior described above was clearly evidenced (Fig. 2), by means of the radiographic evolution of a 58 year-old patient with hip fracture and loss of the mechanical stability by failure of the osteosynthesis, producing non-union and defect of bone substance in the fractured area. The operation included the osteosynthesis replacement and interposition of blocks of coralline hydroxyapatite to fill the defect. After

6 months the patient evolved satisfactorily from the clinical and functional points of view, although the frontiers and location of the blocks of the biomaterial are perfectly observed radiographically. After 3,5 years the place occupied by the hydroxyapatite is now a compact mass with a density bigger than the one in the bone environment without defined frontiers and after 5 years the biodegradation process of the biomaterial is still more intense.

The rate of these events varies from a patient to another depending on the age, the place, type and magnitude of the lesion and on the

auxiliary or complementary treatments.

The figure 3 shows the evolutive radiography of a young patient that presented a relapsed bone cyst in the femur, with antecedents of hopeless surgical treatment with bone graft. The surgical cleaning and curettage of the affected area was practiced and the remainder bone defect was filled with granulated of coralline hydroxyapatite. After 6 months the patient was clinically asymptomatic and after 4 years the implant was not observed, its place has been completely taken by a healthy bone.

It is well known that the different types of tricalcium phosphate biomaterials present different rates of reabsorption depending on their structural composition, cristallinity, solubility, etcetera. The hydroxyapatites of high purity and cristallinity are considered as non-reabsorbables, although changing their composition, the apatites can be obtained with different biodegradation degrees. According to the present experience the biodegradation or reabsorption concept is a relative term for the bone implant biomaterials of calcium phosphates in general. Unfortunately most of the studies carried out, *in vitro* as well as *in vivo* to evaluate these properties comprise relatively short periods of time. The information on the effect of the aging over this type of implant for long periods of time is extremely limited.^{13, 14} In author opinion all the calcium phosphates biomaterials due to their chemical and structural similarity with the mineral support of the bone end up by incorporating to the natural dynamics of the own

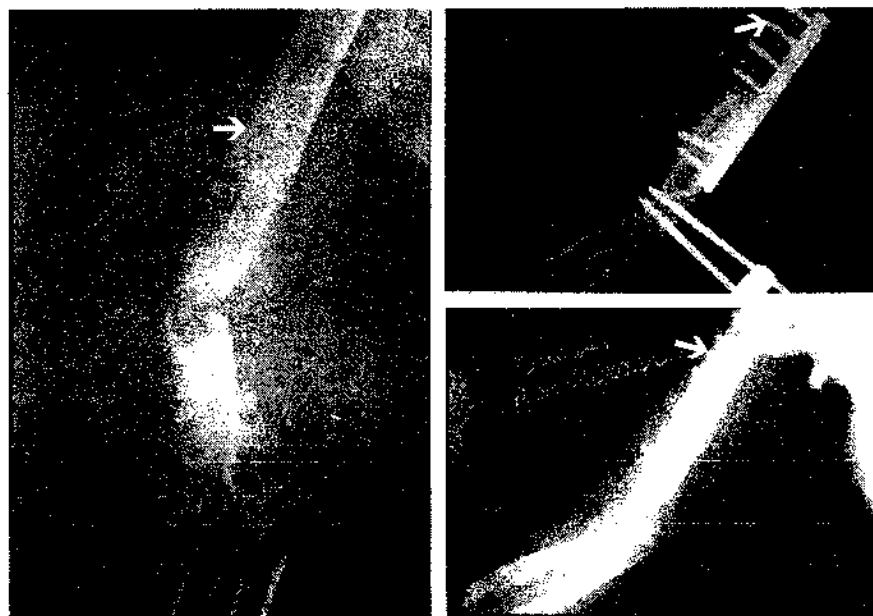


Fig. 1. Atrophic pseudoarthrosis of right humerus. Before the intervention (left), postoperative radiographic control at 6th week (right upper) and after 6 months (right lower) it is observed the consolidation and bone regeneration in the whole region including sequels of the previous screws (arrow).



Fig. 2. Patient with hip fracture and loss of the mechanical stability by failure of the osteosynthesis (1). Osteosynthesis replacement and complement of Coralline Hydroxyapatite in blocks to fill the defect. After 6 months of postoperative evolution (2), after 3,5 years (3) and after 5 years (4).

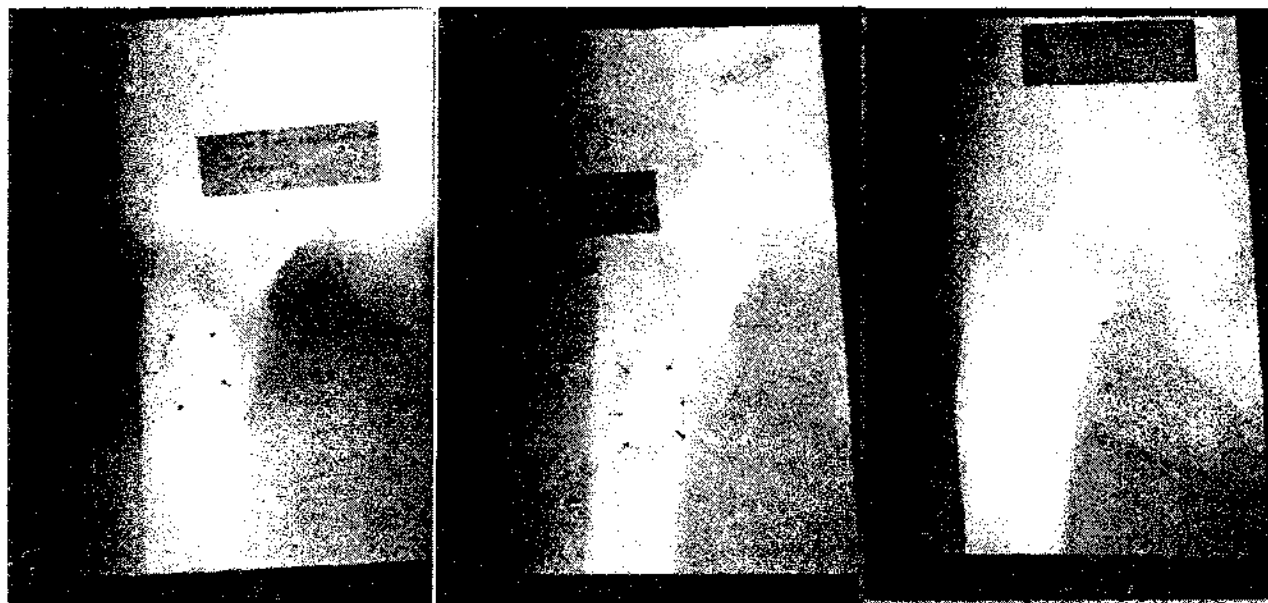


Fig. 3. Patient with a relapsed bone cyst, who was treated previously with autogenous bone graft (left). He received surgical treatment and filling the defect with Coralline Hydroxyapatite. After 6 months of evolution (center) and after 4 years is clinically and radiographically restored (right).

bone tissue. It is the case of the coralline hydroxyapatite HAP-200. The behavior of the biomaterial will depend on the physical-chemical properties of the implants, that's why responses should not be expected to foreign body or another complication throughout the time after its implantation.

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BIBLIOGRAPHY

- González R., Melo M.C. y Rodríguez A.C. Hidroxiapatita porosa HAP-200. Principales características físico-químicas. *Química Nova*, 16, 509, 1993.
- González R., Handal E. y Fernández J. Cinética de la reacción de transformación hidrotérmica del coral a hidroxiapatita. *Química Nova*, 16, 513, 1993.
- Pereda O. y González R. Aplicaciones de la Hidroxiapatita coralina HAP-200 como material de implante óseo en ortopedia. *Biomédica*, 14, 22, 1994.
- Blardoni E., Maestre H. and González R. Coral bioimplants in orthopedic. *Bioceramics*, 11, 599, 1998.
- Ciénega M.A., Lira J.M., Almanza A. y Pulido H. Uso de hidroxiapatita coralina HAP-200 como sustituto de injerto óseo en ortopedia. *Rev. Mex. Ortop. Traum.*, 12, 410, 1998.
- Sanjurjo V., Almarales C. y Alvarez M.C. El coral y la periodontitis. *Avances Médicos de Cuba*, 12, 32, 1997.
- Yuan H., Kurashina K., de Bruijn J.D., Li Y., de Groot K. and Zhang X. A preliminary study on osteoinduction of two kinds of calcium phosphate ceramics. *Biomaterials*, 20, 1799, 1999.
- Jallot E. Correlation between hydroxyapatite osseointegration and Young's Modulus. *Med. Eng. Phys.*, 20, 697, 1998.
- Jensen S.S., Aaboe M., Pinholt E.M., Hjorting-Hansen E., Melsen F. and Ruyter I.E. Tissue reaction and material characteristics of four bone substitutes. *Int. J. Oral Maxillofac. Implants*, 11, 55, 1996.
- De la Caffiniere J.Y., Viehweger E. and Worcel A. Long-term radiologic evolution of coral implanted in cancellous bone of the lower limb. Madreporic coral versus coral hydroxyapatite. *Rev. Chir. Orthop. Reparatrice Appar. Mot.*, 84, 501, 1998.
- Cottrell D.A. and Wolford L.M. Long-term evaluation of the use of coralline hydroxyapatite in orthognatic surgery. *J. Oral Maxillofac. Surg.*, 56, 935, 1998.
- Vuola J., Taurio R., Goransson H. and Asko-Seljavaara S. Compressive strength of calcium carbonate and hydroxyapatite implants after bone marrow-induced osteogenesis. *Biomaterials*, 19, 223, 1998.
- Mahan K.T. and Carey M.J. Hydroxyapatite as a bone substitute. *J. Am. Podiatr. Med. Assoc.*, 89, 392, 1999.
- Ayers R.A., Simske S.J., Nunes C.R. and Wolford L.M. Long-term bone ingrowth and residual microhardness of porous block hydroxyapatite implants in human. *J. Oral Maxillofac. Surg.*, 56, 1297, 1998.

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