Endoret® (PRGF®) Technology
BTI implant system

Scientific Dossier
Introduction

This scientific dossier summarises the series of indexed international articles published over the last 20 years on the range of products and technologies developed by BTI Biotechnology Institute. It highlights the vast amount of scientific evidence that backs the biosafety and effectiveness of plasma rich in growth factors (Endoret® (PRGF®)) in many fields of medicine, with a particular focus on oral and maxillofacial surgery and oral implantology.

This autologous technology has revolutionised the field of personalised regenerative medicine, as with the patient’s blood we can obtain different therapeutic formulations rich in growth factors, the application of which encourages healing and tissue regeneration, reducing pain and inflammation.

Many publications show the predictability and safety of BTI dental implants and of the surgical techniques (sinus elevation, split, biological reaming, etc.) developed under a biological philosophy by Dr. Eduardo Anitua.

This dossier also reviews the therapeutic potential of Endoret® (PRGF®) in other fields of medicine in which our research team has been a pioneer at a worldwide level: orthopaedic surgery, sports medicine, treatment of chronic ulcers and facial rejuvenation, among others.
What are growth factors and how do they act?

Growth factors are a set of substances that carry out an important function in intercellular communication. They carry out a large number of biological functions among which cellular proliferation is important, though they also decisively affect cellular survival, migration, differentiation and even apoptosis.

Growth factors carry out their function at very low concentrations in body fluids and tissues, in the region of pico or nanograms. They act by binding to receptors located on the cell membrane that transmit the signal from the exterior to the interior of the cell, through the coupling of different protein kinases that are phosphorylated and which regulate a signalling cascade that ends up with the activation of one or more genes.

The process of tissue regeneration includes a complex set of biological events controlled by the action and synergy of a cocktail of growth factors. There are three agents involved in tissue regeneration: the cellular component, a combination of multiple biological mediators that include growth factors and cytokines among others and a matrix or “scaffold” that gives the new tissue under construction support.

After an injury or tissue damage, they are activated and coordinate a large number of intercellular or intracellular paths with the aim of restoring the integrity of the tissue and its haemostasis. Growth factors are also necessary to promote angiogenesis or the formation of blood vessels that will supply
oxygen and nutrients to the damaged tissue. Another fundamental aspect to be considered in the regeneration of a tissue is the development of a “scaffold” that acts as a provisional extracellular matrix and therefore houses the cells as well as locally presenting the biochemical, physical and structural signals that allow the anchorage of the cellular motility machinery.


Over the last 20 years, the detailed study of platelets, of the biological mediators they contain and of the formulations aimed at allowing the administration and therapeutic use of growth factors and autologous biomaterials has allowed significant progress and has greatly increased the versatility and therapeutic possibilities of Plasma Rich in Growth Factors (Endoret® (PRGF®)).

Endoret® (PRGF®) technology is based on the preparation of 100% autologous platelet-rich plasma, which when applied to damaged tissue areas speeds up the regeneration of a large number of tissues without any adverse effects. Plasma rich in growth factors (Endoret® (PRGF®)) is a personalised technology that has revolutionised the field of regenerative medicine. This article, published in one of the most prestigious journals in the field of biotechnology, summarises the most important clinical results obtained with Endoret® (PRGF®). Its application over the last decade has extended to many fields of medicine, from oral and maxillofacial surgery to dermatology, cosmetics, orthopaedic surgery and sports medicine, and more recently to ophthalmology.

The biological activity of the different formulations obtained with Endoret® (PRGF®) is based on two fundamental pillars. On the one hand, the content in plasma and in particular platelet growth factors whose action regulates the main processes involved in tissue regeneration.

On the other, the fibrin matrix, which is used as a provisional structure to house the cells and control the release kinetics of the growth factors present in Endoret® (PRGF®).

This article published in the prestigious journal Trends in Pharmacological Science, the most important in the field of pharmacology, talks about the therapeutic potential of Endoret® (PRGF®) and in particular describes how the perfect synergy between growth factors and fibrin is a key aspect when explaining the clinical results obtained with this autologous technology.
The set of therapeutic preparations of Endoret® (PRGF®) are obtained by means of a simple protocol based on a tiny volume of the patient's blood. The blood is centrifuged separating the erythrocytes and white cells from platelet-rich plasma. The two fractions of Endoret® (PRGF®) are separated from the rest of the blood components by means of aspiration using the Plasma Transfer Device (PTD). Later, and prior to its therapeutic application, the fractions of Endoret® (PRGF®) are activated, leading to a series of therapeutic formulations.

This article, published in one of the most important scientific journals in the field of biomaterials, focuses on the enormous versatility of Endoret® (PRGF®), as by using the patient's blood we can obtain up to 4 biocompatible preparations:

a. Endoret® (PRGF®) supernatant: used to cultivate primary cells and stem cells in the laboratory; it is also the base of new eye drops for treating a large number of pathologies of the ocular surface.

b. Liquid Endoret® (PRGF®): Ideal for skin infiltrations, tissues of the musculoskeletal system, TMJ, etc. It is the perfect tool to bioactivate dental implants and prostheses of all types with the aim of accelerating their osseointegration.

c. Endoret® (PRGF®) clot or “scaffold”: Ideal for filling in defects and promoting tissue
regeneration: post-extraction sockets, treatment of ulcers, tissue engineering, etc.

d. Fibrin membrane: due to its haemostatic properties it is the best biomaterial for sealing defects and stimulating epithelisation.


Endoret® (PRGF®) is the first 100% autologous platelet-rich plasma to be described in literature worldwide. It is, likewise, a pioneering technology in translational regenerative medicine. Over 20 years of research, added to its exclusive properties, make Endoret® (PRGF®) a unique technique. Endoret® (PRGF®) is prepared with small volumes of the patient’s blood and does not require the use of thrombin or chemical agents for its activation. Unlike other products, it does not include white blood cells (leukocytes) in its composition, which gives it more effective anti-inflammatory properties. It is the most versatile technology, as its multiple formulations offer a large number of therapeutic applications.

In short, as shown by the series of letters to the editor published during recent years, we can define Endoret® (PRGF®) as a platelet-rich autologous plasma whose effectiveness and safety have been widely proven. However, it is important to remember that not all platelet-rich plasmas are Endoret® (PRGF®).


The pillars of Endoret® (PRGF®): growth factors

Endoret® (PRGF®) contains a cocktail of autologous growth factors that come from both the plasma and the platelets. In fact, the platelets have a complex storage system in the form of intracellular granules that allow them to transport a large number of biologically active molecules. According to some authors, this list of proteins and peptides can come close to 500 molecules. Alpha (α) granules are the most abundant as there are around 40 to 80 alpha granules per platelet, but they are also the ones with the greatest retention capacity. In addition, they contain a series of antibacterial proteins that are generically called thrombocidines and are lethal to a large variety of bacterial species. However, it is important to remember that the plasma contains important growth factors and that the combination of the plasma and platelet factors is a key element in the biological action of Endoret® (PRGF®).

In a couple of revision articles, our research team along with the Nurden Doctors from the Reference Centre for Platelet Disorders in France have characterised the protein content of platelets in order to learn about the set of molecules present in Endoret® (PRGF®) formulations.

Platelets release substances that promote tissue regeneration and modulate both angiogenesis and inflammation. Important factors include platelet-derived growth factor (PGSF), transforming growth factor β (TGF-β), basic fibroblast growth factor (bFGF), vascu-
lar endothelial growth factor (VEGF), epidermal growth factor (EGF) and angiopoietin-1. They release in parallel antibacterial molecules and specific growth factors that act on the mobilisation of progenitor cells from the bone marrow or from peripheral niches.

Calcium acts as a cofactor in the activation process of Endoret® (PRGF®), which allows the conversion of the fibrinogen of the plasma into fibrin, generating a gel or clot with important biological functions. On the one hand, fibrin is an excellent matrix to maintain and house the cells, it acts as a provisional scaffold while the definitive tissue is regenerated and acts as a continuous growth factor release system. It is therefore a biocompatible and autologous sponge full of growth factors and cytokines that will permit a progressive release of them during several weeks.


In over a decade of preclinical research, during which tens of cellular phenotypes were studied, we have managed to discover and understand the multiple biological functions that the set of therapeutic formulations of Endoret® (PRGF®) carry out. The biological mediators of Endoret® (PRGF®) stimulate and encourage such important processes for tissue regeneration as cellular proliferation and migration, chemotaxis (or the call from a distance for cells to go to the injury site), inflammation and the auto/paracrine synthesis of new molecules with biological activity.


The growing interest in the range of biological options that Endoret® (PRGF®) offers has even reached the field of stem cells. Stem or progenitor cells are characterised on the one hand by their unlimited capacity for proliferation, and on the other by the possibility of undergoing asymmetrical division (that is, self-renewal) maintaining their stemness while at the same time they can differentiate to diverse types of cells. There are different types of stem cells depending on their origin and their anatomical location.

There is evidence that the content of biologically active agents in Endoret® (PRGF®) affects the mobilisation, adhesion, proliferation, survival, activation and differentiation of mesenchymal stem cells and other subtypes of precursor cells.

In addition, the cocktail of growth factors of Endoret® (PRGF®) is an ideal resource for culturing and expansion of stem cells in the laboratory.


How does Endoret® (PRGF®) act?

The use of growth factors and autologous fibrin for regenerative purposes represents a new approach to personalised medicine that a large number of patients could benefit from.

In this paper, published in one of the most important journals of drug delivery, they discuss the mechanisms of action through which Endoret® (PRGF®) produces its multiple therapeutic effects.

The stimulation of cell proliferation and migration along with the call to circulating cells to come to the location of the injury are basic aspects of the action of Endoret® (PRGF®). Likewise, also important is the angiogenic action of the growth factors which is crucial to start regeneration. Last of all, though no less important, its anti-inflammatory and antibacterial properties are a key element.

Our research team has proven that Endoret® (PRGF®) presents bacteriostatic activity with a large number of bacterial and fungal strains. This is because the platelets contain a series of antibacterial proteins called thrombocidines. These proteins are part of a wider family known as defensins, and they are of a cationic nature, which will allow them to bind to and alter bacterial membranes. In addition to thrombocidines, platelets transport and release other antimicrobial peptides among which we should mention platelet factor 4, RANTES, connective tissue activating peptide 3, the basic protein of platelets, thymosin β-4, and fibrinopeptides A and B.
In a recent paper we could see that the bacteriostatic potential of platelet-rich growth factors is due both to the antimicrobial peptides and to the fibrin, and not to the presence of leukocytes in their composition. In fact, the bacteriostatic effect of Endoret® (PRGF®) is identical to that of a platelet and leukocyte-rich plasma. Another important conclusion of this study was to confirm how the inclusion of leukocytes notably alters the structure and uniformity of the fibrin matrix.


This revision article is a reference in international bibliography as it is the journal with the greatest scientific impact. It is about the therapeutic potential of platelet-rich plasma and, in this specific case, Endoret® (PRGF®). The use of growth factors and autologous fibrin for regenerative purposes represents a new approach to personalised medicine that a large number of patients could benefit from.


This dossier summarises the preclinical and clinical scientific articles that endorse the biosafety and efficacy of Endoret® (PRGF®) in many fields of medicine.
The fibrin obtained with Endoret® (PRGF®) is probably the best biomaterial for encouraging tissue regeneration.
The objective of this study was to characterise for the first time the proteins existing in the Endoret® (PRGF®) clot, which are in contact with the fibrin network. The technology of proteomics was used to identify proteins, their gene ontology, and network mapping of these proteins.

The results confirmed that Endoret® (PRGF®) is a clot composed primarily of fibrin proteins, forming a macroscopic three-dimensional (3D) network. In addition to the results obtained, they provide a description of the catalogue of key proteins that are in close contact with the fibrin matrix. The lists of proteins obtained are grouped into families and networks according to the gene ontology. An enrichment can be seen in certain proteins that are key to tissue regeneration, such as thrombospondin 1, fibronectin and vitronectin.

The most relevant channels involved were also catalogued for the proteins identified, finding an enrichment in canonical channels important for tissue regeneration, such as acute phase proteins.

Lipid metabolism proteins presented a high level of enrichment (13 times that of the control). Thus, a basic catalogue of proteins has been established that may be used as basis for future research. Taking the data as a whole, an enrichment was found in the proteins and families of proteins that take part specifically in tissue regeneration and in wound healing.
The objective of this study was to characterise the kinetics of the release of four growth factors (GFs) (VEGF, PDGF-AB, HGF and IGF-I) from matrices of Endoret® (PRGF®) fibrin. Similarly, a comparison was made with those obtained using a PRP with leukocytes (L-PRP) to determine the effect of the inclusion of said cells on the release of the aforementioned morphogens, including an inflammatory cytokinin (IL-1β) in this analysis.

The results showed that both preparations differed only in the leukocyte content (0.3 x 10^3/µl in the Endoret® (PRGF®) as opposed to 5.7 x 10^3/µl in the L-PRP); the enrichment in platelets was similar. The morphological analysis of the Endoret® (PRGF®) matrix demonstrated its fibrillar composition. The interweaving of the fibres give this matrix a high porosity. Regarding the GF release kinetics, 70% of PDGF-AB is released during the first three days, while in the case of the other GF analysed, there is a quicker initial release (60-70%) during the first 24 hours. In all cases there is then a stage of slow sustained release. The release kinetics in all cases comply with a diffusion model applying the Korsemeyer-Peppas equation. After eight days, a significant percentage of these GF were retained inside the matrix (approximately 20-30%). The effect of the presence of leukocytes in the platelet-rich plasma was assessed at 24 hours. With the exception of one of the donors, no significant alterations were evident in the concentration of GF released by both matrices. Nevertheless, a drastic in-
crease in the concentration of IL-1beta was detected in the incubation medium. The Endoret® (PRGF®) matrices release approximately 70% of the GF they contain during the first 3 days, and 30% is retained a week after the formation of the clot. Therefore, the use of Endoret® (PRGF®) ensures the availability of this GF during the different stages of the tissue regeneration process, thus backing the effectiveness of this autologous therapy. Furthermore, the addition of leukocytes would drastically increase the concentration of IL-1beta at the injury site, which could favour inflammatory processes, as this cytokinin is one of the main cytokinins responsible for mediating the pro-inflammatory effects.
The objective of this *in vitro* study was to determine the potential of different formulations obtained with Endoret® (PRGF®) Technology to stimulate cell proliferation, migration and adhesion, and the synthesis of angiogenic factors and various components of the extracellular matrix. In addition, the ability of this autologous technology to impede and inhibit the myo-differentiation induced by the transforming growth factor beta 1 (TGF-β1) was evaluated. The primary cultures of human gingival fibroblasts were characterised by specific markers (vimentin, CD90 and type I collagen) using immunofluorescence. The results obtained showed that Endoret® (PRGF®) significantly increases the cell proliferation and migration. In addition, this technology significantly stimulates the cell adhesion of the gingival fibroblasts to a matrix of collagen I. This autologous technology also stimulates the synthesis of vascular endothelial growth factors (VEGF), hepatocyte growth factors (HGF), and hyaluronic acid (HA). The results obtained in this study confirmed that Endoret® (PRGF®) is able to inhibit and reverse the myofibroblast phenotype. The persistence of this biological phenotype can severely affect tissue function, giving rise to a fibrotic tissue that impedes its normal functioning.

Thus, we can conclude, that Endoret® (PRGF®) technology effectively promotes the regeneration of the gingival connective tissue, stimulating the main biological processes involved in the repair and providing an
interesting focus for gingival situations characterised by chronic persistent inflammation and elevated levels of TGF-β1.

The loss of alveolar bone can affect both function and aesthetics for the patient. The osteoblasts are the main cells involved in the repair and regeneration of bone tissue. This study evaluated the stimulatory effect of Endoret® (PRGF®) on the alveolar osteoblasts. For this purpose primary cultures of alveolar osteoblasts were used. They were previously characterised by immunofluorescence revealing markers of bone origin (osteopontin, osteocalcin and alkaline phosphatase). The effect of different formulations of Endoret® (PRGF®) on aspects of cells such as proliferation, migration and protein synthesis, involved in the most important processes of tissue regeneration. The results showed that the treatment with Endoret® (PRGF®) increased the proliferative capacity of the alveolar osteoblasts. Similarly, the different formulations tested significantly increased the cell migration process and chemotaxis. In addition, a stimulating effect of Endoret® (PRGF®) on the synthesis of the angiogenic growth factors analysed was quantified. Regarding the formation of extracellular matrix, again the different formulations stimulated the synthesis of procollagen I and osteocalcin, principal components in the bone matrix. Endoret® (PRGF®) also stimulated the enzyme alkaline phosphatase, involved in the mineralisation of said matrix, in particular after 11 days of treatment. All of the findings of this study indicate the safety and efficacy of Endoret® (PRGF®) technology in bone regeneration, by the stimulation of key processes such as proliferation, migration, chemotaxis.
and the synthesis of molecules with an angiogenic and antiinflammatory effect as well as extracellular matrix components.

The regeneration of the periodontal tissue is one of the most important goals in treating periodontal disease. The purpose of this in vitro study was to evaluate the biological effects of Endoret® (PRGF®) technology on human fibroblasts of the periodontal ligament. To do so, primary cultures were obtained of fibroblasts from the human periodontal ligament, characterised by immunofluorescence with connective tissue markers (type I collagen, fibronectin and periostin) and an osteogenic marker (osteopontin). The cell response to treatment with Endoret® (PRGF®) in different biological processes, such as cell proliferation, migration and adhesion, was studied, as well as its effect on the stimulation of the secretion of different biomolecules and the expression of integrin α2 by periodontal ligament fibroblasts cultured on type I collagen.

The results obtained showed that Endoret® (PRGF®) significantly stimulates the proliferation and migration of periodontal ligament fibroblasts. In addition, the cells treated with this biological therapy adhered significantly earlier. Moreover, the cell synthesis of different key proteins involved in tissue regeneration, such as vascular endothelial growth factors (VEGF), thrombospondin 1 (TSP-1), connective tissue growth factors (CTGF), hepatocyte growth factors (HGF) and type I pro-collagen were stimulated significantly after treatment with Endoret® (PRGF®). Finally, when the cells were treated with this technology the expression of the integrin α2 was...
lower in comparison with the unstimulated cells. This is because the condition of the cells cultured with Endoret® (PRGF®) is more dynamic. In fact, it has been demonstrated that cell mobility inversely correlates with the expression of the integrins α1 and α2.
Bisphosphonate-related osteonecrosis of the jaw is a common problem in patients subject to long-term administration of highly powerful nitrogenous bisphosphonates. This pathology occurs by means of mechanisms that affect the bone and soft tissue. Zoledronic acid (ZA) is the most powerful nitrogenous bisphosphonate. The objective of this study was to evaluate the role of different concentrations of ZA on the cells of the oral cavity as well as the potential of Endoret® (PRGF®) to overcome the negative effects of this medicine. Primary gingival fibroblasts and primary alveolar osteoblasts were used, both of human origin. To evaluate the effect of ZA, the cell proliferation, apoptosis and the expression of the nuclear kappa beta factor (NF-kB) and phosphorylated nuclear kappa beta factor (pNF-kB) were quantified. The ZA had a cytotoxic effect on the gingival fibroblasts and alveolar osteoblasts. This medicine inhibited cell proliferation, stimulated apoptosis, and induced inflammation. The addition of Endoret® (PRGF®) was effective in suppressing all of these negative effects of ZA. Endoret® (PRGF®) is a cytoprotector against the negative effects of zoledronic acid on the primary oral cells. Thus Endoret® (PRGF®) can be an effective therapy for both preventing and treating bisphosphonate-related osteonecrosis of the jaw.

The application of Endoret® (PRGF®) inhibits the side effects of apoptosis and inflammation induced by zoledronic acid in bone and gingival cells.
This study evaluated the antimicrobial effect of plasma rich in growth factors, Endoret® (PRGF®), on different strains of microorganisms from the oral cavity. After obtaining informed consent, blood was extracted from a total of 17 adult patients who were going to be subjected to a surgical operation in the oral cavity. The blood was extracted and centrifuged, then the millilitre of plasma that is just above the red fraction was collected, but without including the leukocytes. The concentration of platelets and leukocytes was analysed in each of the samples obtained. The different microorganisms used in this study were isolated from patients with oral or dental infections. The most representative microorganisms that colonise and affect the oral cavity were selected, including E. faecalis, C. albicans, S. agalactiae, S. oralis and P. aeruginosa. The antimicrobial effect of Endoret® (PRGF®) was assessed by calculating the minimum inhibitory concentration (MIC). To do this, a concentration of 1x10^4 CFU/ml of each bacterial strain was incubated in different wells with different seried dilutions of Endoret® (PRGF®) for each patient. These were incubated for 24 hours at 37°C. The MIC values correspond to the concentration of Endoret® (PRGF®) present in the last well in which bacterial growth was observed. The minimum bactericidal concentration (MBC) was also assessed; this corresponds to the minimum concentration of Endoret® (PRGF®) necessary to kill a given bacterial strain. The results showed that Endoret® (PRGF®) inhibited the growth of all the bacterial species.
studied at platelet concentrations 3 or 4 times lower than those observed in the samples of Endoret® (PRGF®), except for P. aeruginosa for which an inhibitory effect was not observed. Moreover, the results obtained in this study showed that, except in C. albicans, the different samples analysed produced a bacterial effect at a platelet concentration similar to that found in the samples of Endoret® (PRGF®) in the microorganism species analysed. Endoret® (PRGF®) is a potentially useful product in the fight against post-operative infection. These could represent a valuable quality of Endoret® (PRGF®), in addition to stimulate tissue regeneration.

Regenerative Potential of Endoret® (PRGF®) in odontology

Preclinical Research

In 2009 one of the first pre-clinical experimental studies was performed to determine the regeneration potential of Endoret® (PRGF®). The study was carried out on goats in which cavities with a diameter of 3 mm were prepared in the tibia, simulating artificial alveoluses that were then filled with Endoret® (PRGF®) or with a blood clot (control group). The regeneration of the defect was evaluated 8 weeks after the surgery, by means of histological preparations the newly formed bone was studied and a histomorphometric analysis of the tissue was performed. In the Endoret® (PRGF®) group, it was possible to histologically differentiate trabecular-type newly formed bone surrounded by densely vascularised connective tissue. In the control group, the tissue found in the histologies consisted of connective tissue with a high cellularity with some small areas of intramembranous bone tissue. Thus, Endoret® (PRGF®) can be effective in stimulating the regeneration of bone defects.

a) Bone obtained from one alveolus treated with Endoret® (PRGF®).
b) Bone obtained from one control alveolus

The Endoret® (PRGF®) clot is ideal for filling in the post-extraction alveolus and for releasing growth factors that promote its regeneration.
The objective of this randomised clinical trial was to evaluate the effectiveness of Endoret® (PRGF®) in tissue regeneration in the post-extraction alveolus and in the preparation of oral areas for the subsequent placement of dental implants.

The study included 20 patients who needed dental extractions and dental implant placement. These patients randomly received treatment with Endoret® (PRGF®), or the control treatment without Endoret® (PRGF®). In three additional patients, a split-mouth study was performed.

Between weeks 10 and 16, the biopsies were taken and they were then analysed. The results showed that the epithelisation of the 10 patients treated with Endoret® (PRGF®) was very good or excellent in comparison with the control. The regeneration of the alveolus treated with Endoret® (PRGF®) was almost complete in 8 of the 10 patients. The biopsies showed an external bone regeneration, forming a compact bone with well-organised trabeculae.

In patients with severe defects that were treated with Endoret® (PRGF®) and autologous bone, a greater bucco-lingual/palatal width was achieved. In the control group however, connective tissue and very little mature bone were observed. The epithelisation, in 100% of the cases was complete and significantly better than in the areas not treated with Endoret® (PRGF®).
The regeneration of mature bone was also greater in terms of amount and bone quality in the patients treated with Endoret® (PRGF®).
To verify the efficacy and safety of treating the post-extraction alveolus with Endoret® (PRGF®), a randomised double-blind clinical trial was designed in which the post-extraction alveolus in molars of the mandible would be regenerated during a period of 12 weeks. For this purpose a total of 60 patients were recruited and divided into the Endoret® (PRGF®) treatment group (36 patients) and the control group (24 patients).

The principal variable studied was the percentage of alveoluses that achieved 75% volume of regenerated bone in the alveolus at the end of the follow up. As secondary variables the following were also evaluated: the bone density (measured in Hounsfield units with a CT scan), soft tissue epithelisation index (scale from 1 to 5), thickness of keratinised gum, post-operative pain (on a visual analogue scale) and inflammation (scale from 0 to 3). In addition bone and soft tissue biopsies were taken in the patients in whom after the follow-up period dental implants were placed, using this surgery to take the samples.

The defects to be treated after the randomisation corresponded to molars with radicular septum in 54.16% in the control group, while only 38.9% of the defects of the treatment group preserved the septum. Due to this difference the defects of the Endoret® (PRGF®) group were of a greater volume than those treated in the control group. In the group treated with Endoret® (PRGF®)
The application of Endoret® (PRGF®) reduces inflammation and pain, accelerates the epithelisation of soft tissues and promotes bone regeneration.

a regeneration volume greater than or equal to 75% was achieved in 96.67% of the cases, while in the control group this percentage was only reached by 45.45%, which was a statistically significant difference (p<0.01).

The percentage of newly formed bone measured in the histology was 63.08% for Endoret® (PRGF®) compared to 35.56% for the control group. The density of the newly formed bone was greater in the treatment group (average 450 UH) compared to the control group (average 318 UH), and these were statistically significant differences.

In the evaluation of post-operative pain after three days, pain was experienced by 18% of the patients (in the treatment group), and by 62% in the control group with statistically significant differences in both groups. After seven days the pain had disappeared in the Endoret® (PRGF®) group, and there was pain in 15% of the control group. The pain at 15 days was absent in both groups.

In the evaluation of the inflammation index after three days, the presence of inflammation was found in 18% of the cases in the Endoret® (PRGF®) group, while in 65% of the cases in the control group it was present, and these were statistically significant differences. After seven days, inflammation persisted in 39% of the cases in the control group, while in the study group it had disappeared completely. These differences were statistically significant.
After 15 days the inflammation had disappeared in both groups.

The epithelisation rate evaluated at three, seven and 15 days was greater with statistically significant differences in the Endoret® (PRGF®) group compared to the control group. The following figure shows one of the cases included in the study in the control group compared to another case included in the Endoret® (PRGF®) group.

The thickness of the keratinised gum observed in the case of Endoret® (PRGF®) was the double that of the control cases, and the epithelial crests were thicker.

Clinical efficacy of Endoret® (PRGF®) promoting the regeneration of the post-extraction alveolus.
In this study the efficacy of Endoret® (PRGF®) in improving the healing of the post-extraction alveolus was evaluated in diabetic insulin-dependent patients.

A split-mouth clinical trial was performed: The post-extraction alveolus was treated with Endoret® (PRGF®), while the other acted as a control and was subject to natural healing without treatment. The selection of each treatment was randomised. A total of 34 patients subject to bilateral extractions of homologous teeth were included. In general, for both treatment types, no surgical complications such as excessive bleeding, infection or alveolar osteitis were observed. The value observed on the tissue healing index was always ≤ 8, and the complete closure of the alveolus was of on average on day 21, for approximately 50% of the patients. The comparison between the relative values, in the experimental and control areas, showed better healing and quicker closure for the area treated with Endoret® (PRGF®), with statistically significant differences on days three and seven and the limit of the difference at 14 days. The pain score on the VAS was practically equal on both sides, reaching zero after four days for the area treated with Endoret® (PRGF®) and after the sixth day for the control area without Endoret® (PRGF®). The results of patient questionnaire were unanimously in favour of treatment with Endoret® (PRGF®). The small samples of patients with blood sugar values of at least 240 mg/dl showed a poorer healing score and less reduction in the alveolus volume. The authors
concluded that the application of Endoret® (PRGF®) after dental extractions improves the healing process in the diabetic patients, accelerating the final closure of the alveolus (epithelisation) and the maturation of the tissue, which proves the link between the use of Endoret® (PRGF®) and improved wound healing in diabetic patients.
The extraction of teeth is the main cause of bisphosphonate-related osteonecrosis of the jaw (BRONJ). This evidence has led to the study of Endoret® (PRGF®) in preventing the development of BRONJ after a dental extraction. To study this, 176 patients were recruited who took zoledronic acid and required the extraction of teeth. The patients were randomised in two groups: the first (91 patients) received the Endoret® (PRGF®) treatment while the second (85 patients) were used as the control group. The Endoret® (PRGF®) treatment includes filling in the post-extraction alveolus with a clot rich in growth factors and covering the surgical area with a fibrin membrane before closing the flap. X-rays and CT scans were taken before surgery and 60 months after. No intra-operative complications were observed in either of the two treatment groups.

Endoret® (PRGF®) was shown to be effective in preventing the development of BRONJ in 542 extractions. There were no clinical or x-ray signs of any BRONJ lesions. On the other hand, in the control group 5 out of 267 extractions developed a BRONJ lesion as indicated by the presence of a bone exposure. The average period for the development of this lesion is 91.6 days after the tooth extraction. All of the patients who showed these osteonecrotic wounds had multiple myeloma, and they were all taking zoledronic acid (for more than 12 months). At the same time, at the time of diagnosis of BRONJ in the control group, the five patients had not yet completed
The application of Endoret® (PRGF®) in the treatment of the post-extraction alveolus prevents the development of BRONJ in patients treated with bisphosphonates.

their cycles of chemotherapy with vincristine. All of the cases of BRONJ were treated surgically and, during the bone extirpation surgery, Endoret® (PRGF®) was used with excellent results.

*Tooth extraction in patients on zoledronic acid therapy. Mozzati M, Arata V, Gallesio G. Oral Oncol. 2012 Sep;48(9):817-21.*
The objective of this study was to identify the surgical protocols that can improve the regeneration of the post-extraction alveolus in patients who have received radiotherapy in the head or neck.

The study was designed as prospective split-mouth study. A total of 20 patients who needed a bilateral extraction of paired teeth were included. The post-extraction alveolus of the side that received the radiotherapy was the experimental group. This alveolus was treated with Endoret® (PRGF®) while the alveolus on the other side acted as the control (blood clot). The study variables were the residual volume of the alveolus, the healing index, pain, and surgical complications. The variables were evaluated in 4 sessions until 30 days after the surgery and were analysed statistically.

The group of the alveoluses treated with Endoret® (PRGF®) showed better values of the residual alveolus volume and healing index in all of the follow-up sessions (statistically significant differences). Thus the regeneration of the mucous membranes in the Endoret® (PRGF®) group was quicker than in the control group. No complications were observed in the experimental group while in the control group two cases of bone exposure were observed. This bone exposure was treated successfully with Endoret® (PRGF®).

A correlation was observed between the residual volume of the alveolus and the dose...
of radiation received but not with the time passed since the radiotherapy.

It has been tested that Endoret® (PRGF®) is effective in the treatment of the patients who have received radiotherapy in the head and neck, accelerating the regeneration of the mucous membranes and preventing post-operative bone exposure.

The aim of this study was to evaluate the potential effect of Endoret® (PRGF®) in the lateral approach for sinus elevation.

Five patients were included who required bilateral sinus elevations with a residual bone height of 1-3 mm. On one of the quadrants Endoret® (PRGF®) was used along with inorganic bovine bone, while only biomaterial was used on the other side. The use of Endoret® (PRGF®) doubled the volume of the graft thanks to the action of the fibrin. Post-operative pain and inflammation were greater on the control side (without Endoret® (PRGF®)). The sinuses treated with Endoret® (PRGF®) presented a larger amount of new vital bone than in the control area. The immunohistochemistry of the biopsies revealed that the number of blood vessels per square millimetre of connective tissue was 116 vessels as opposed to 7 in the control areas. These results showed the therapeutic potential of Endoret® (PRGF®) for reducing inflammation, increasing new bone formed and generating blood vessels in these sinus elevation procedures.

The effectiveness of Endoret® (PRGF®) in reducing tissue inflammation (anti-inflammatory properties) and improve bone formation in maxillary sinus elevations.
The objective of this clinical trial was to evaluate whether the use of Endoret® (PRGF®) during maxillary sinus elevations could have a favourable impact on the pain and other factors related to the patient’s quality of life in the first week after surgery. A total of 30 patients (18 women and 12 men) were included in the study, 15 in the experimental group and 15 in the control group. There were no significant differences with regard to the age, gender distribution and smoking habits between the two groups. The height of the residual crest was similar in the two groups (3.9 ± 1.3 mm and 4.1 ± 1.1 mm in the experimental and control groups, respectively). In the Endoret® (PRGF®) group one intraoperative perforation of less than 5 mm was made in the Schneider membrane and in two cases in the control group. In the case of the Endoret® (PRGF®) group, the perforation was resolved using an Endoret® (PRGF®) membrane. The use of Endoret® (PRGF®) responded with a significant reduction of perceived pain during the second and third day post-op, in comparison with the control group. The patients in the group treated with Endoret® (PRGF®) presented significantly less inflammation, fewer haematomas and less discomfort when chewing and speaking throughout the assessment period. Opening the mouth and sleeping were better in the patients treated with Endoret® (PRGF®) for the first 3 to 4 days. Regarding absence from work, no differences were detected between the two groups. Bleeding was significantly less in the first 2 days in the Endoret® (PRGF®) group.
Moreover, significantly fewer analgesics were taken in the Endoret® (PRGF®) group in comparison with the control in the first three days. The authors concluded that adding the application of Endoret® (PRGF®) to the procedure for maxillary sinus augmentation had a beneficial effect on the patients’ quality of life in the early post-surgical stage.

The objective of this study was to describe a minimally invasive technique for the restoration of rear atrophic maxillae with a bone residual height < 5 mm.

The transalveolar sinus elevation was performed using sequential drilling in which the last mm of bone above the Schneider membrane was prepared with a front cutting drill. For the elevation of the membrane and its protection, an Endoret® (PRGF®) fibrin plug (very well retracted fibrin membrane) was inserted upon creating a window of 50% in the base of the alveolus. The results indicated that the bone residual height was 4.04 ± 0.09 mm. The treatment protocol described significantly increased the residual bone height to an average of 8.86 ± 1.60 mm. These indicates a bone gain of 4.82 mm. The bone height data was analysed according to the type of graft: Endoret® (PRGF®) alone or Endoret® (PRGF®) + bone graft. The bone gain was similar in both groups (statistically non-significant differences). Thus, Endoret® (PRGF®) is an effective biomaterial as a bone graft.

The post-operative period of the patient was good, without major surgical complications, indicating the efficacy and safety of Endoret® (PRGF®). This technique can constitute a minimally invasive alternative for treating the atrophic posterior maxillae.

The objective of this study was to evaluate the effectiveness of Endoret® (PRGF®) in a new surgical technique for restoring narrow alveolar crests in the anterior of the maxilla. The use of Endoret® (PRGF®) was also assayed as a biomaterial for bone regeneration. The study included 11 patients who needed a sinus elevation and also presented a horizontal loss at anterior level that would require an increase.

In this area, the window obtained from the sinus (after performing the lateral sinus elevation) was positioned and secured using BTI microscrews. The space between the graft and the alveolar process was sealed with autologous bone (obtained by means of biological drilling) mixed with Endoret® (PRGF®) or with the Endoret® (PRGF®) clot. This was all covered with an autologous fibrin membrane from the patient before closing the flap.

No inflammation or infection was reported or observed. Neither the donor nor the receiving area displayed any dehiscence of the incision.

X-ray analysis showed an initial crest width of 3.57 ± 0.46 mm (range 1.96-6.05 mm). The use of block grafts from the lateral wall of the maxillary sinus was effective in achieving a statistically significant gain of 5.34 ± 1.59 mm (range 2.56-8.10 mm) in the horizontal dimension of the area restored. The total increase percentage achieved was between 42% and 200%, with a mean value of 180.6%.

The objective of this study was to evaluate the use of extra-short implants in conjunction with Endoret® (PRGF®) to treat severe atrophy in the mandible. Ten patients presenting severe reabsorption in the posterior sectors of the mandible were recruited. The treatment plan included covering the exposed surface of the implant that exceeded the upper edge of the jaw with a hybrid biomaterial composed of Endoret® (PRGF®) and autologous bone. This combination stabilises the graft and creates a bell shape around the implant to favour vertical bone growth. As a result, the residual height from the bone crest and the mandibular canal was 4.19 ± 0.97 mm. The application of Endoret® (PRGF®) favoured the stability of the bone graft around the implant and induced a vertical bone gain of 1.6 ± 0.5 mm around the implant. The post-operative period for patients was favourable as no surgical complications were reported. After five months, a provisional implant-mounted prosthesis was fitted following a progressive-load protocol. None of the extra-short implants failed. The surgical technique used in conjunction with the application of Endoret® (PRGF®) may be a minimally invasive alternative to bone increase surgery (block graft).

The application of autologous bone graft + Endoret® (PRGF®) to cover the exposed surface of extra-short implants induced the vertical bone growth around the implant. This technique may be an alternative to the use of block grafts to increase bone in severely atrophic maxillae.
The objective of this randomised clinical trial was to evaluate the effectiveness of Endoret® (PRGF®) in preventing the exposure of the titanium mesh in bone increase surgery. The inclusion criteria were the presence of a bone height ≤ 7mm, a thickness of the alveolar process ≤ 3 mm or both, in the maxilla or the mandible. The patients were randomly assigned to receive the treatment with or without Endoret® (PRGF®). The Endoret® (PRGF®) membrane was placed over the titanium mesh before closing the flap.

In total, 43 alveolar bone increases were performed, placing 97 implants using ABB as the graft material in all of them. Approximately 15 patients received treatment with Endoret® (PRGF®), while the other 15 acted as a control.

Significant differences were found between the two groups, in terms of complications and amount of bone formed. In the control group, 28.5% of the cases suffered exposure of the mesh, while in the Endoret® (PRGF®) group, no exposure was recorded. The bone increase was greater in the Endoret® (PRGF®) group than in the control. 97.3% of the implants placed in the control group and 100% of those placed in the Endoret® (PRGF®) group were successful for 24 months.

The objective of this study was to evaluate the efficacy of Endoret® (PRGF®) in improving the bone regeneration around the ABB in lateral elevations of the maxillary sinus. Approximately 87 patients (residual bone height < 7 mm) were recruited for this randomised clinical trial. The study groups were ABB and ABB plus Endoret® (PRGF®) (ABB + PRGF). A total of 286 implants were placed in the increased bone, and were monitored for 24 months. The perforation of the Schneider membrane was reported in 5 patients (2 in the control group and 3 in the experimental group). This perforation was treated with Endoret® (PRGF®) or with a collagen membrane depending on the treatment group. The effectiveness of treating the membrane perforation with Endoret® (PRGF®) indicates that is a safe biomaterial, effective in the management of the perforation of this membrane. The survival rate of the implants was 96.2% and 98.6% for ABB and ABB + Endoret® (PRGF®) respectively.

In addition, a split-mouth comparison was performed in five patients with bilateral maxillary atrophy. The histological and histomorphometric analysis revealed that the formation of new bone was significantly greater in the group ABB + Endoret® (PRGF®).

The aim of this study was to clinically evaluate the ridge expansion technique with ultrasonics called the Split-Crest technique, for the placement of dental implants in patients with narrow ridges, together with the application of Endoret® (PRGF®) in tissue regeneration. At least 6 months after loading the implants, the state of the hard and soft tissues and the expansion achieved were evaluated, as well as the survival rate of the implants. Fifteen patients were included whose previous average ridge width was 4.29 mm and who received a total of 37 BTI implants. In surgery, Endoret® (PRGF®) was applied to aid the regeneration of the tissues and the implants were humected with Endoret® (PRGF®) to accelerate osseointegration. The results showed that the state of the soft tissues was very good with adequate values of plaque index, bleeding and probing depth. The survival rates of the implants between 11 and 28 months after insertion was 100%. The average bone expansion achieved was 3.35 mm. These results showed how the Split-Crest technique with ultrasonics along with the application of Endoret® (PRGF®) can be considered an effective and safe technique for bone expansion in narrow ridges.
This paper describes an innovative ridge expansion technique called Split-Crest in 2 stages, indicated for patients with extremely resorbed ridges (3-4 mm) in conjunction with the application of Endoret® (PRGF®) to aid the regeneration of the bone and soft tissue. It consists of an expansion carried out in 2 consecutive stages using transitional implants. Three patients received 4 implants with this technique. To do so, surgery was performed with ultrasound and transitional implants (2.5 and 3.0 mm in diameter) were used and replaced, 5-7 months after its placement, by implants with larger diameters. The average follow-up period was 20.5 months. During the surgery Endoret® (PRGF®) was used. The state of the soft tissues was good with adequate probing depth values (average value was 3.06 mm). The average bone expansion achieved after the procedure was 8.49 mm apical and 7.10 mm occlusal. There were no implant failures during the follow-up period. These preliminary results prove the predictability and safety of the two-stage Split-Crest technique combined with the application of Endoret® (PRGF®) and its potential use in patients with severely resorbed ridges, as well as avoiding the use of other more aggressive techniques such as bone grafts.

The objective of this study was to evaluate the effect of plasma rich in growth factors (PRGF) on pulp regeneration and apex formation in necrosed teeth with an open apex. After accessing and cleaning the root canal, the triple antibiotic paste was inserted into the canal to disinfect it. After 2 weeks, apical bleeding was caused manually using a file with a diameter of 80. The rich part of the PRGF was activated and injected to fill the canal up to the level of the enamel-cement joint. The tooth was temporarily restored. The patients were revaluated after 2 weeks. If the tooth was now asymptomatic, the canal would be sealed with MTA and the tooth restored with composite. At 22 months post-op, total closure of the apex was observed in two teeth. In another two teeth a closure of the apex and an increase in the thickness of the root wall were observed.

Thus, the protocol described in this study has shown that PRGF may be a suitable scaffold for pulp regeneration. Clinical trials are necessary to evaluate the effectiveness of PRGF in pulp regeneration.

The objective of this study was to evaluate the effectiveness of Endoret® (PRGF®) in the treatment of osteoarthritis of the temporomandibular joint. Thirteen patients (mean age: 47.64 ±7.51 years, 11 were women) who suffered osteoarthrosis of the temporomandibular joint (TMJ) were selected. The variables studied were the maximum mouth opening (in mm) and the pain (visual analogue scale). The data was gathered before treatment (t0), after 30 days (t1) and after 6 months (t2). The data was analysed statistically (the Student t-test for paired variables). The pain evaluation indicated a reduction from 7.69 ± 1.9 (t0) to 1.54 ± 1.74 (t1) and 0.23 ± 0.65 (t2). This reduction was statistically significant. The maximum mouth opening experienced an increase of 7.38 mm in t1 (from 30.15 ± 4.44 mm (t0) to 37.54 ± 5.10 mm (t1)). This increase was statistically significant. At t2, the maximum mouth opening was 39.54 ± 4.55 with an increase of 9.38 ±2.21 since t0 and 2 mm since t1. Both differences were statistically significant.

Thus, the intra-articular use of Endoret® (PRGF®) is an effective procedure for controlling pain and improves the mobility of the TMJ in patients with osteoarthrosis of this joint.

The objective of this pilot clinical trial was to evaluate the use of Endoret® (PRGF®) in the management of the Schneider membrane during maxillary sinus elevations. Eight maxillary sinus elevations were carried out in eight patients.

In the sinus elevation procedure, there were two perforations of the Schneider membrane during the procedure, which were effectively resolved using a clot of Endoret® (PRGF®). The post-operative quality of life of the patient was generally good.

Biphosphonates are a group of drugs that reduce the rate of bone turnover, mainly through the inhibition of the action of osteoclasts, and they are administered both orally and intravenously in patients with oncological or rheumatic treatments.

A side effect of these medicinal products is the development of exposed bone that does not heal in the maxillofacial region in patients treated with bisphosphonates. For this reason this pathology was named bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Recently, the use of Endoret® (PRGF®) has been proposed for the treatment of BRONJ as part of a preventive and therapeutic approach.
Osteoradionecrosis (ORN) is the worst long-term complication of radiotherapy in the head and neck. This study evaluates the safety and the effectiveness of Endoret® (PRGF®) in the treatment of ORN.

A series of 10 patients with ORN were treated with the excision of necrotic bone and the application of Endoret® (PRGF®) to improve and accelerate the regeneration of the soft tissues. A clinical and x-ray evaluation of the patient was performed up to 12 months after the surgery. The pain was evaluated during the first week after surgery. The maturation and quality of the regeneration of the tissues were evaluated according to the modified healing index.

All of the patients were successfully treated with Endoret® (PRGF®). No intra or post-op complications were observed. The clinical and x-ray evaluation revealed the absence of signs of infection or exposed bone up to 12 months after surgery. The maturation and quality of the regenerated tissue was excellent. Complete closure of the defects was obtained in all the patients. The pain and muscular trismus was low in all of the patients despite all of the patients stopping taking analgesics from third day after surgery.

The objective of this clinical trial is to compare the fibrin adhesive and Endoret® (PRGF®) as haemostatic agents. Approximately 120 patients with different blood disorders were randomised to receive out-patient dental extractions. Before the surgery, the patients received systemic haematological treatment. In the control group (fibrin adhesive) 106 extractions were carried out (7 were for impacted third molars). Secondary bleeding was observed in 3/60 patients (5%) on the third day after surgery, and an additional surgical operation and systemic treatment were necessary. These additional measures were repeated on day 7, after the surgery, in one of the three cases. In the Endoret® (PRGF®) group there were 98 dental extractions (23 were impacted third molars). Secondary bleeding was observed in two patients (3.3%) on the first day after the extraction. Homeostasis was reestablished with surgery but without systemic treatment. Four of the five secondary bleeds were in patients with haemophilia A. Thus, Endoret® (PRGF®) was as effective as the fibrin adhesive. Nevertheless, Endoret® (PRGF®) is of autologous origin, does not require additional systemic treatment when treating the post-extraction alveolus, improves the neo-angiogenesis, reduces morbidity and also the cost for the health system.

In this article a patient developed a BRONJ lesion after being treated for several years with zoledronic acid (IV) and after a tooth extraction. Their symptomatology included severe pain and hemimandibular paraesthesia due to affectation of the dental nerve. The treatment consisted of surgical resection of the necrotic bone area combined with the application of Endoret® (PRGF®).

One month after surgery, total closure of the ulcerous lesion in the mucous membrane was observed without the presence of necrotic bone. Six months later, a significant improvement of the pain and paresthesia was observed. After a year, the patient had totally recovered sensitivity and the absence of necrotic bone was confirmed. These clinical results support the use of Endoret® (PRGF®) as an adjuvant treatment for patients with BRONJ. The use of this autologous technology is based on the potential effects of the growth factors released and the fibrin on bone remodelling and on angiogenesis.

The application of Endoret® (PRGF®) in the treatment of BRONJ improves the closure of soft tissues and the regeneration of the bone defect.
The chemistry and the topography of the surface are of the utmost importance for the osseointegration of dental and orthopedic implants inserted in load-bearing areas. This study evaluated in vitro and in vivo titanium implants whose surface was modified with calcium ions (UnicCa® surface). The calcium ions have caused a long-lasting chemical and nano-topographic modification of the titanium oxide. The analysis of the composition of the most superficial UnicCa® layer with the secondary ion mass spectrometry technique indicated that the calcium ions protected the implant surface from the passivation of titanium oxide with hydrocarbons. The release of calcium ions from the UnicCa® surface was also studied. Two thirds of the calcium were released during the first minute. The rest of the calcium ions were released over 85 days. In cell cultures, the surface modified with calcium ions significantly increased the adhesion, proliferation and differentiation of the osteoblasts. The insertion of the implants in the tibia of ewes showed that the UnicCa® surface very significantly increased the bone-implant contact and the bone density in an area of 1 mm around the implant. Thus, the UnicCa® surface represents an instrument for improving and accelerating the osseointegration of dental implants.

*Effects of calcium ions on titanium surfaces for bone regeneration. Anitua E, Piñas L, Murias A, Prado R, Tejero R. Colloids Surf B Biointerfaces. 2015 Jun 1;130:173-81*
This paper presents the results of research carried out on the release of growth factors using surfaces bioactivated with Endoret® (PRGF®).

The principal result of this study was that to achieve a sustained release and, therefore, better regeneration around the implant, Endoret® (PRGF®) must be activated. Two activators of the coagulation cascade were tested: calcium and thrombin ions. Calcium, in addition to avoiding a potential immune response, allows a greater release of platelet growth factors. In short, this paper indicates the importance of the bioactivation of the implant with Endoret® (PRGF®) in improving osseointegration.

This biomechanical study was carried out with the aim of evaluating the influence of distal offset on the stress distribution that the bone around the implant sustains. A mesial force of 200 N and a distal force of 230 N were applied to the prosthesis. The results showed that the fact that there is a limited offset (of up to 2.5 mm) of the prosthesis on the implant does not increase stress on the adjacent bone.

A controlled offsetting of the implant on the prosthesis, in addition to allowing an optimal aesthetic restoration and reducing the emergence profile, does not increase bone stress and a possible risk of implant failure.

The use of larger diameter implants will reduce even further the stress in the bone adjacent to the implant.

The aim of this biomechanical study was to evaluate the influence of the length, diameter and geometry of BTI implants on bone stress distribution. 3D finite element models were created and a load of 150 N was applied at an angle of 30 degrees. Different diameters (3.5 to 5.0 mm) and lengths (8.5 to 15 mm) were evaluated. The results showed that the effect of the implant diameter on bone stress distribution was more significant than the effect of the length or geometry. On the other hand the maximum stress was located around the implant neck and most of it in the bone adjacent to the first threads. According to the results observed, the use of greater diameter implants can be beneficial to reduce stress around them, meaning that the use of short implants with a greater diameter could be a reasonable alternative in locations where residual bone height is limited.
The objective of this study is to evaluate the sequential regeneration around dental implants with different configurations and surfaces.

Approximately 12 Beagle dogs were subjected to the extraction of all teeth, from the second premolar to the first molar, on both sides of the mandible. After 3 months a full-thickness flap was raised and two implants of different systems and different surfaces were inserted in the premolar area on one side of the mandible. The two surfaces evaluated in this study were unicCa® by BTI and T3® by 3i. The surgery on the other side of the mandible and the slaughter of the animals was organised in order to obtain biopsies that represent the regeneration at 2, 4 and 8 weeks (6 biopsies for each time).

The results indicated that the sequential regeneration patterns around the surfaces unicCa® by BTI and T3® by 3i were similar. Nevertheless, a greater percentage of newly formed bone was stimulated by the UnicCa® surface by BTI than by the surface T3® by 3i. The differences were statistically significant at 2 and 4 weeks.

The osseointegration of dental and orthopedic implants is the reason for their success in clinical practice. Titanium is the material of choice for the manufacture of these implants due to its favourable properties. After the placement of the implant, the titanium surface establishes an ionic balance with the adjacent tissues. In this balance, calcium plays a fundamental role since it is a co-factor in the coagulation cascade, intermediating in the adsorption of plasma proteins and intervening in numerous processes at an intra- and extracellular level relevant for bone regeneration. In this trial the objective was to study the modification of the titanium surface with calcium ions (the UnicCa® surface). The UnicCa® surface was characterised in both in vitro and in vivo models. Compared with the unmodified surface, the UnicCa® surface was super-hydrophilic and was capable of inducing platelet activation and adsorption and clot formation upon contact with plasma. In an in vivo model, the UnicCa® surface had significantly improved the peri-implant bone volume and bone density at 2 weeks and the implant-bone contact at 8 weeks after insertion, in comparison with the unmodified surface. Furthermore, the combination of the UnicCa® surface with Endoret® (PRGF®) produced significantly greater bone-implant contact at 2 weeks after implantation. These findings suggest the importance of the formation of a provisional matrix in osseointegration and reinforce the potential of the UnicCa® surface for improving the osseointegration of the implant.
In this study carried out with research animals the aim was to determine whether the humectation of the implant surfaces with Endoret® (PRGF®) encouraged their osseointegration. To this end a total of 23 implants were inserted in the tibia/radius of 3 goats; 13 of them were previously humected with Endoret® (PRGF®) while the other 10 were not (control). Eight weeks later, a histomorphometric analysis was carried out on the bone biopsies of the sacrificed animals and we observed that the value of the bone-implant contact (BIC) was 51.28% in the animals humected with Endoret® (PRGF®), as opposed to 21.89% in the implants that were not humected, generating a significantly greater area in the former (p<0.01).

These results prove how the humectation of implants with Endoret® (PRGF®) encourages their faster osseointegration.

Humectation of BTI implants with Endoret® (PRGF®) encourages faster osseointegration.
This study carried out on research animals evaluated the effect of humectation of dental implants with Endoret® (PRGF®) to encourage and accelerate their osseointegration. To this end, two dogs were used in which 12 implants were inserted, 6 on each side of the mandible, humecting the implants of one side with Endoret® (PRGF®), and placing the implants of the opposite side without humectation (control). After 12 weeks, the implants were extracted along with the adjacent bone for a histological-histomorphometric analysis. The results showed that the implants humected with Endoret® (PRGF®) presented higher levels of BIC (bone-implant contact). We also observed higher values of trabecular bone thickness and bone maturity in the areas treated with Endoret® (PRGF®).

The aim of this study was to assess both the morphology and the composition of the interface formed by the implants activated with Endoret® (PRGF®). Both features are of capital importance for later regenerative events as both the morphology and the composition of the interface allow the modulation, among other aspects, of the balance between inflammation and regeneration around the implant. In this article we could see through electron, atomic and confocal microscopy that the bioactivation of implants with Endoret® (PRGF®) generates a three-dimensional network with a multitude of platelets, proteins and growth factors. In addition, the composition of the interface of the surfaces bioactivated with Endoret® (PRGF®) is specific, containing platelet and protein elements different to those of other surfaces assessed. The specificity of both the morphology and the composition of the interfaces formed with implants bioactivated with Endoret® (PRGF®) is very possibly the reason behind its beneficial clinical results.

The aim of this randomised clinical trial was to assess the need or not to administer an antibiotic prophylaxis with 2 g of oral amoxicillin one hour before the single dental implant insertion surgery to avoid post-op infections. Twelve private centres which recruited a total of 105 patients took part; 52 received amoxicillin and 53 received the placebo.

After 6 months, there were 6 infections and 2 implant failures in each group. No statistically significant differences were found for post-op infections, adverse events or implant failures between both groups. Observing the results of this study, antibiotic prophylaxis for single implants may not be necessary.
The objective of this study was to describe and compare the conventional drilling system at high revolutions (1200 rpm with external irrigation) to a biological drilling system at low revolutions (50-100 rpm) that allows recovery of the autologous bone for use as a bone graft. In the protocol of biological drilling: except the initial drilling (800 rpm with irrigation), the preparation of the implant site was carried out at low revolutions without irrigation. The design of the diameter drills generates retentive turns able to retrieve the bone particles during drilling. The microscopic examination showed that the bone structure and the presence of live cells was preserved in all the samples collected with low-revolution drilling while these qualities were not maintained with conventional drilling. The drilling temperature, working at 50 rpm without irrigation, was approximately 28°C indicating the safety of this new drilling protocol. In the clinical trial, the optimum stability of the implants after 4 months in the bone with a graft of autologous bone from drilling + Endoret® (PRGF®) indicates the good regenerative quality of this graft. Biological drilling at low revolutions can reduce damage to the host tissue and can be used to obtain a mass of live bone ideal for carrying out bone grafts associated with Endoret® (PRGF®).
The quality of receiving bone is one of the most decisive factors for the osseointegration of the implant. In this paper, the bone density and the cortical bone thickness were the two parameters used to classify the bone type into five categories. The bone type was used to decide the drilling protocol with the aim of ensuring a suitable level of primary stability. The study included 295 implants with a length of 8.5 mm inserted in 192 patients. The results indicated that the insertion torque was of $59.29 \pm 7.27$, $56.51 \pm 1.62$, $46.40 \pm 1.60$, and $34.84 \pm 2.38$ Ncm for bone type I, type II, type III and type IV, respectively. Thus, we can see that the insertion torque varies depending on the bone type; it is greater for bone with a higher density. The drilling protocol of this study was effective in obtaining an insertion torque greater than 30 Ncm in the low-density bone (bone type IV). In addition, we observed that bone with a density below 400 Ncm is different from the rest in bone type IV. In fact, the resistance of the bone to drilling was notably lower and the insertion torque was only 5 Ncm. The x-ray analysis indicates the absence of cortical bone and that it was present in the posterior area of the maxilla. Therefore, we have named this bone type V.

Maxillary sinus elevation by means of osteotomy with ultrasound.

This article describes the sinus elevation technique with the use of an osteotomy with ultrasonics. This is the first job that uses surgical ultrasonics. This technique offers important advantages over a conventional osteotomy that uses diamond tool bits. In addition, it reduces the risk of perforating Schneider’s membrane. On the other hand it improves the vision and hygiene of the surgical area and provides a more conservative and controlled bone incision.

When there is a limited mesio-distal space, the distal offset of the implant position to replace a single tooth in the posterior area may be an option. The objective of this study is to evaluate it in the long term in the posterior area.

Approximately 31 patients were treated with a single implant inserted in an off-centre position in the posterior area. The prosthetic restoration was performed in using the Bipilar® by BTI and a cemented prosthesis.

Some 34 implants were placed in this study. In the study group 20 patients were women and the average age was 56 ± 12 years. The follow-up period for the implants, from loading, was up to 10 years (Average: 4 ± 3 years). The majority of the implants were placed in bone type II in the molar area (85%). The adoption of an off-centre configuration and an implant with a greater diameter resulted in a mesial bone loss of 0.85 ± 0.57 mm and a distal loss of 0.83 ± 0.68 mm. There was only one implant that failed, 4 months after insertion. Thus survival rate of the implants was 97.1%. No prosthetic complications were observed.

The aim of this study was to analyse the factors that affect the stability of dental implants at 12 weeks after insertion, measured by means of resonance frequency analysis using the Osstell system.

In this prospective clinical trial, 235 implants were inserted in 93 patients. The prediction variables collected were grouped into variables patient, implant and operative variables, and the baseline implant stability quotient (ISQ). They were analysed in a multivariate model to determine its influence on the ISQ score 12 weeks after insertion (result variable). No link was found between the patient variables and the ISQ values at 12 weeks. Among the implant variables, it was observed that the ISQ value at 12 weeks was lower for the implant with a narrow diameter ($P < 0.001$) and the dental implants in the superior maxilla ($P = 0.006$). Among the variables of the surgical technique, the use of Endoret® (PRGF®) ($P = 0.011$) gave the best ISQ values at 12 weeks. Thus, the implant diameter, its location and the application of Endoret® (PRGF®) significantly affect the stability of the implants.


This study was carried out with the aim of describing the immediate-load dental implant insertion technique and to evaluate the long-term survival, as well as the possible risk factors related to its failure. A total of 1139 implants were included and a survival rate of 99.3%, 96.8% and 96.9% was observed for the analysis based on the implant, on the surgery and on the patient, respectively. Only 5 of the implants failed during the follow-up period and no failure-related risk factors were found.

These results showed the predictability of the immediate load technique described provided it is used with appropriate insertion torques and following strict clinical protocols.

The aim of this study is to describe a regeneration technique using Endoret® (PRGF®) to preserve the architecture of the soft tissue around the immediate post-extraction implant.

A 30-year-old woman came to the clinic with clinical symptoms that worsen when chewing in the area of the second right premolar. After creating a flap without relieving incisions, the presence of a vertical fracture was confirmed. After the tooth was extracted, a BTI dental implant was inserted immediately.

The space between the bone and the implant was filled with a graft of Bio-Oss® and Endoret® (PRGF®). Then the implant was covered with a dense fibrin matrix and it was sutured and left exposed.

This technique enabled guided bone regeneration, without the need for vertical relieving incisions, thus avoiding the emergence of gingival scarring. The appearance of the gingival edge was aesthetically acceptable. Thus, it was possible to satisfy the aesthetic needs without the need for more surgery or grafts. The integration of this technique into clinical practice will aid the achievement of ideal aesthetic results.

The objective of this clinical trial was to evaluate short implants in posterior areas of the superior maxilla and mandible area in the long term.

The patients included in this retrospective study had received one or more short implants (≤ 8.5 mm long) in posterior areas, at least 10 years earlier. All the implants were previously humected with plasma rich in growth factors (Endoret® (PRGF®)). The accumulated success rate was the primary study variable. The crestal bone loss and the influence of different variables were evaluated as secondary results of the study. A total of 111 short implants (7.0, 7.5 and 8.5 mm long) were evaluated, placed in 75 patients. Some 94 implants were spliced to other longer implants. The average follow-up time was 123.3 months (SD = 10.4 months). The average crown-implant ratio was 1.4 (SD = 0.3). The average MBL was of 1.0 mm in the mesial (SD = 0.7) and 0.9 mm (SD = 0.6) in the distal. One short implant failed during the study follow-up period. The success rate was 98.9% and 98.2% for the implants and the patients, respectively. Thus, the use of short implants is a safe and effective long-term option.

The objective of this clinical trial was to evaluate a new minimally invasive surgical technique for the restoration of the mandible with severe atrophy, avoiding the need for a major surgical restoration.

In this technique, the biological drilling protocol was carried out in two stages: the first phase with conventional drills, limiting the working length to 1 mm less than the length of the alveolus to prepare. In the second phase, a front cutting drill was used to prepare the last 1 mm of the alveolus to avoid damaging the inferior dental nerve.

With this technique, 114 extra-short implants humectated with Endoret® (PRGF®) were inserted into 72 patients. The average follow-up period was 26 months from implant insertion. No signs of impaired nerve function were observed in the lower dental nerve. The implant survival rate was 98.4%. The peri-implant bone loss was 1 mm. No prosthetic complications were observed during the observation period.

Thus, the extra-short implants humectated with Endoret® (PRGF®) are an effective minimally invasive alternative in the prosthetic restoration of atrophic inferior maxillae.

The objective of this prospective study was to evaluate the clinical success of placing short implants in combination with a transcrestal sinus elevation, complemented with platelet-rich plasma without leucocytes. Endoret® (PRGF®) was used to reduce the risk of perforating the Schneider membrane and other possible surgical complications. A total of 65 implants were placed in 25 patients. The short implants were spliced to one or more standard implants.

After a mean follow-up time of 14.4 months, 60 implants in 23 patients were evaluated. The success and survival rates of the implant were 100%.

There were no failures in any of the prosthetic restorations performed. The bone loss around the implant (a year after loading) was $0.34 \pm 0.21$ mm for short implants of 8.5 mm ($n=25$) and $0.36 \pm 0.30$ mm for the longest implants ($n=35$). There were no significant differences between the two groups ($p=23$).

Thus, the treatment protocol proposed is a viable option for the restoration of posterior atrophic maxillae.

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The aim of these studies was to evaluate the long-term survival (up to 8 years of follow-up) of short and extra-short BTI implants (≤ 8.5 mm) in posterior areas of the superior maxilla and the mandible. In the first of them, a total of 1287 short implants placed in 661 patients were included. The results showed a survival rate of 99.3% and 98.8% for the analysis based on the implant and on the patient, respectively. Nine of the implants failed due to different causes. No risk factors related to the failure of the short implants could be identified.

In the second study the extra-short implants (≤6.5) were also studied separately, showing survival rates of 97.9% and 97.1% for the implants and patients, respectively.

These results showed that treatment with short and extra-short implants can be considered a safe and predictable technique if used following strict clinical protocols.
This study was carried out with the aim of evaluating the influence of an unfavourable crown/implant ratio (≥1) and other variables of the implant, be they surgical, prosthetic or biomechanical, on Marginal Bone Loss and on the survival of short implants in posterior areas. A total of 128 implants placed in 63 patients were evaluated. The average follow-up period was 22 months. The average C/I ratio of the implants was 1.82. In 86 of them it was <2 and in 42 implants ≥2. The marginal bone loss observed was 0.35 mm during the first year post-load and 0.45 mm after the first year post-load. The implant and prosthesis survival rate was 100%. The unfavourable C/I ratio did not show any relationship with the marginal bone loss of the implants. Of the remaining variables studied, the only one that showed a negative influence was the use of cantilevers in prosthetic rehabilitations.

The use of short and extra-short implants is generating prosthetic restorations with unfavourable implant-crown proportions. This study evaluates the repercussions that this unfavourable crown-implant proportion may have on the marginal bone loss. It also identifies possible ratios that endanger the success of implant-mounted restorations.

This study included 34 patients with 45 extra-short implants (length of 5.5 or 6.5 mm). The follow-up time was up to 4 years with an average of 2 years. The crown-implant ratio was 2.4 (range: 1.5-3.69). The crown height space (CHS), defined as the distance from the bone crest to the occlusion plane, was 17.05 ± 3.05 mm. None of the extra-short implants failed.

The results indicate that the type of antagonist significantly affected the marginal bone loss. This was greater when the antagonist is a fixed bridge (1.28 ± 1.09 mm) and lower when the antagonist is a natural tooth (0.73 ± 0.60 mm) or complete prosthesis (0.89 ± 0.60 mm). Nevertheless, the crown-implant ratio does not significantly influence the marginal bone loss. A significant correlation was observed between the CSH and the marginal bone loss.

This study was carried out to evaluate the long-term survival and clinical effectiveness of narrow-diameter (2.5 and 3.0 mm) BTI Tiny® implants in patients with an insufficient ridge (2.5 to 4.0 mm) to allow the placement of standard-diameter implants. 51 patients were included who received a total of 89 implants. The results showed a survival rate of 98.9% and 98.0% for the analysis based on the implant and on the patient, respectively. Only one implant failed 12 months after its placement. Average bone loss after 2 years of implant load was 1.26 mm. These results showed that 2.5 and 3.0 mm Tiny® implants can be used effectively and safely for the treatment of narrow and severely resorbed ridges.

The use of implants with a small diameter (<3.75 mm) are a minimally invasive alternative to procedures of horizontal bone increase. The objective of this study is to analyse the long-term results of the Tiny® 2.5 mm implant in a restoration with a fixed prosthesis.

The patient records were analysed retrospectively to select those who had at least one Tiny® 2.5 mm implant before July 2005. The variables studied were the demographic parameters, the peri-implant bone loss, the survival of the implants and the prosthetic complications. Thirty-seven implants were placed in 20 patients (mean age: 54.05 ± 9.7 years). The follow-up time of the implants was 6.5 ± 3.2 years (range from 0 to 9.7 years). This follow-up time was greater than 7 years for 22 implants. Only one implant failed due to the lack of osseointegration. Only two prosthetic complications were observed (fracture of the connector and porcelain). Thus, the survival rate was 97.3% for the implants and 92.0% for the prostheses. The peri-implant bone loss was <1 mm.

Thus, the use of the Tiny® implant to support a fixed prosthesis obtains favourable long-term results.

“The many clinical studies carried out with BTI implants prove their versatility, safety and predictability”
This study aims to describe a protocol and analyse the results of the immediate replacement of the implant that has failed due to periimplantitis.

The BTI atraumatic implant extraction kit was used. All of the implants were extracted by applying a countertorque with the specific wrench designed for this purpose. Then a new implant was placed in the same socket and in the same surgical intervention after the application of Endoret® (PRGF®). The new implants were monitored to evaluate their survival and the crestal bone loss.

Seventeen patients (mean age 58 ± 10 years) were included for the replacement of 22 implants. Of the new implants, one failed 16 months after insertion, which resulted in a survival rate of 94.7%. The average follow-up time was 40 ± 16 months after insertion. The mesial and distal bone loss was 0.89 ± 0.62 mm and 0.97 ± 0.66 mm, respectively.

Thus, the use of the implant extraction kit is minimally invasive so it is possible to insert the new implant immediately. The results of this study enable us to recommend this protocol in the treatment of failed implants.
Preclinical Research was carried out to evaluate the mechanisms of the atraumatic explantation of dental implants, which can make it possible to place a new one in the bone socket.

Twelve dental implants were placed in the diaphysis of the tibia and, once osseointegrated, they were explanted using the BTI of implant extraction kit. The osseointegration and explantation of the implant were evaluated using the value of the implant stability quotient, the extraction torque and the angular offset. The bone walls of the alveolus and the surface of the extracted implant were analysed under a conventional microscope and a scanning electron microscope. The osseointegration of the implant broke with an angular offset of less than 20°. The value of the implant stability quotient after breaking the osseointegration was similar to its value when the implant was inserted. At the same time, the explantation technique was minimally invasive, causing minimal damage to the bone structure and its cellularity.

Thus, the atraumatic extraction of the dental implant and the maintenance of the viability and structure of bone socket resulting from the explantation make it possible to achieve optimum conditions for the osseointegration of a new implant inserted in this socket.

The objective of this study is to evaluate the effectiveness of BTI implant extraction kit in the treatment of failed implants.

The implant was extracted by applying a counter-torque to the implant-bone interface. The post-explantation socket was inspected and cleaned to remove the granulation tissue. The immediate insertion of a new implant was carried out when suitable primary stability could be achieved.

Some 81 patients were treated to remove 158 failed implants in the maxilla and mandible. The average age of the candidates was 62 ± 11 years. The principal cause of the implant removal was periimplantitis (131 implants; 82.9%) followed by poor positioning of the implant (22 implants; 13.9%). The explantation of 139 implants was achieved at a torque of 146 ± 5 Ncm without the need to use trephine drills. Nevertheless, the use of these drills was necessary to extract 19 implants and the explantation torque was 161 ± 13 Ncm.

All of the implants with a titanium plasma spray (TPS) surface treatment were extracted due to periimplantitis and the explantation torque was less than the implants treated using acid-etching, blasting with particles or oxidisation. The post-operative period of the patients presented no complications. The explantation technique used in this study was effective in preserving and not damaging the oral tissues.
Thus, the protocol described in this study could constitute a real alternative to other traumatic techniques of extracting dental implants. The type of surface treatment of the implant could influence the value of the extraction torque and the periimplantitis.

This article describes for the first time the concept of “de-osseointegration” of implants. For this purpose a new technique has been developed that uses the BTI Explantation Kit, which facilitates an easy and atraumatic explantation while keeping the walls of the alveolar socket intact to allow the placement of a new implant.

In this study a total of 58 explantation cases of different implants were included using the BTI Explantation Kit. The removal torque varied between 80 and 200 Ncm. In 20 cases a new implant was placed. This article shows how the possibility of explanting dental implants atraumatically opens new doors in oral implantology.

This study was carried out with the aim of describing and evaluating the new technique for the atraumatic explantation of implants. This new technique facilitates a fast explantation, keeping the alveolar socket walls intact and at the same time facilitating the insertion of a new implant during the same surgical operation.

In this study 91 implants explanted from a total of 42 patients were included. The removal torques varied between 80 and 200 Ncm. In those cases where the implant removal torque exceeded 200 Ncm, 2-3 mm incisions were carried out with a set of atraumatic trephines to avoid excessively high torques. These results showed how the possibility of explanting implants atraumatically can be considered a viable alternative to replace failed implants.


• Anitua E, Begoña L, Orive G. Clinical evaluation of split-crest technique with ultrasonic bone surgery for narrow ridge expansion: status of soft and hard tissues


Revision articles

- Vaquerizo V, Sánchez M, Padilla S, Orive G, Anitua E.


**Preclinic Research**


Publications

Traumatology, orthopaedic surgery and sports medicine


Clinical Research


- Sanchez M, Anitua E, Andia I. Application of Autologous Growth Factors on Skeletal Muscle Healing. 2nd World Congress on Regenerative Medicine, May 18-20, 2005, Leipzig, Germany.
Endoret® (PRGF®) technology has been a pioneer proving its effectiveness in the treatment of osteoarthritis and tendinopathies.


Publications

Traumatology, orthopaedic surgery and sports medicine


Preclinical Research


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• Anitua E, Pino A, Orive G. Plasma rich in growth factors promotes (PRGF) promotes skin regeneration by stimulating dermal fibroblast proliferation, migration and biosynthetic activity regardless the age of the patient. JWC. 2016

Publications
Dermatology


• Anitua E, Pino A, Orive G. Plasma rich in growth factors promotes (PRGF) promotes skin regeneration by stimulating dermal fibroblast proliferation, migration and biosynthetic activity regardless the age of the patient. JWC. 2016


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