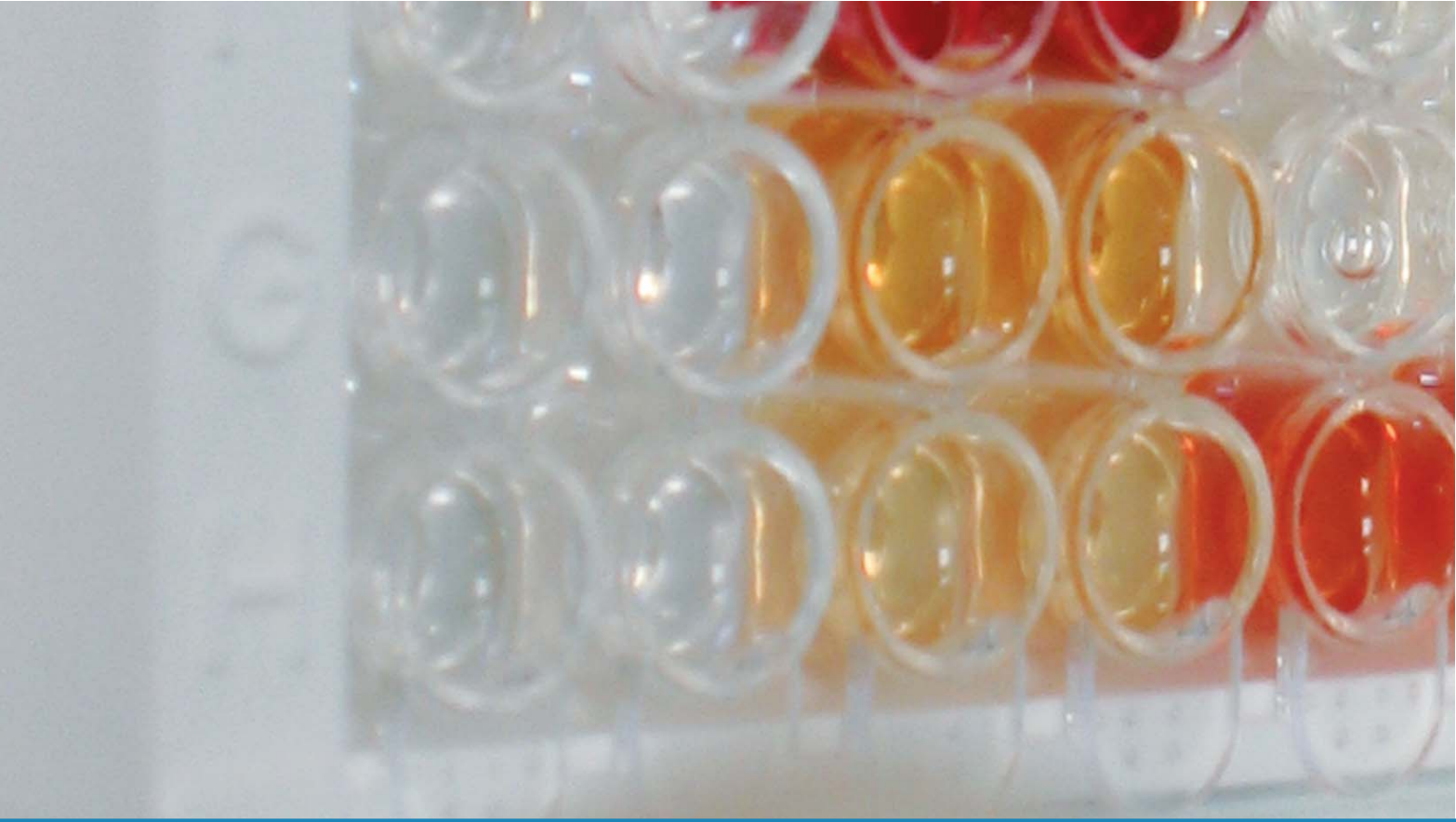
PRGF Technology

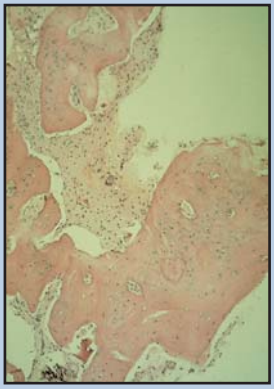
"Prince Felipe Award on Technological Innovation"

Premios Príncipe Felipe a la Excelencia Empresarial

Bti® Biotechnology Institute

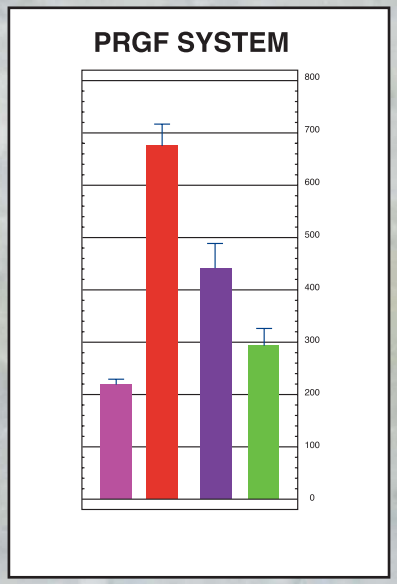


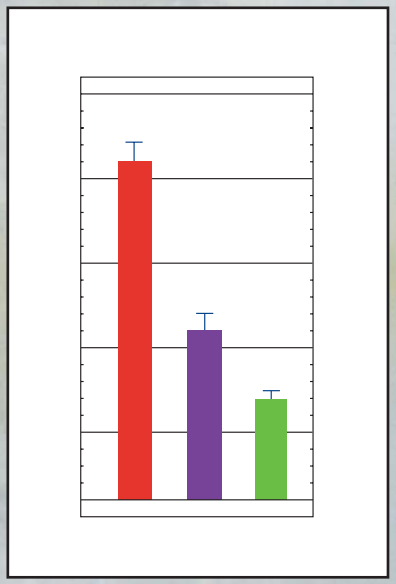
What are Growth Factors?



>> Growth Factors (GFs) are proteins which perform a key role in the complex processes of tissue repair and regeneration.

>> When used in surgeries, GFs promote a fast response that accelerates the regeneration injured tissues.





>> GFs are proteins that have an essential role in the healing process and tissue formation. Their mode of action is to bind to the extracellular domain of a target receptor thereby activating the intracellular signalling cascade.

>> GFs trigger biological effects such as directed cell migration (chemotaxis), angiogenesis cellular proliferation and differentiation, all of which are key events in repair and regeneration processes.

>> GFs are located in blood plasma and inside the platelets, stored in alpha-granules, where there are relevant concentrations of growth factors.

>> Which are the GFs directly involved in tissue regeneration?

--- PDGF: platelet derived growth factor.

--- TGF-ß: transforming growth factor-ß1.

--- bFGF: basic fibroblast growth factor.

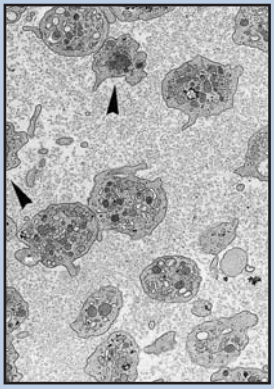
--- VEGF: vascular endothelial growth factor.

--- EGF: epidermal growth factor.

--- IGF-I: insulin-like growth factor type I.

--- HGF: hepatocyte growth factor.

What is the PRGF System®?



>> First system in the world designed exclusively for obtaining PRGF and autologous fibrin.

>> Maximum output: two different products with extraordinary biological activity (PRGF / autologous fibrin).

With a small amount of blood, we can significantly improve treatment.

* Regulations on professional qualificaton necessary for blood extraction may vary depending upon the country.

>> PRGF System enables the obtention of an autologous plasma rich in growth factors from small volumes of blood (from 5 c.c. up to as much as is necessary), adjusting the extracted blood volume to the size of the defect to be treated*.

>> It can be prepared in an office environment in an easily reproducible way.

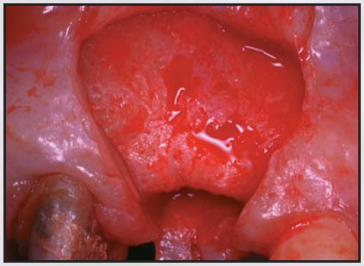
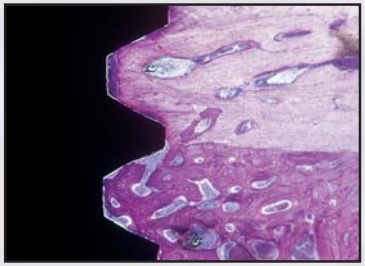
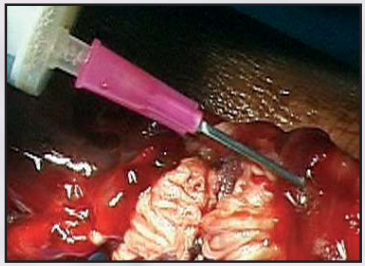
>> Preparation takes between 15 and 20 minutes.

>> No antigenic effect; this is the only described and patented technique in which it is not necessary to use bovine thrombin or any other hemoderivative.

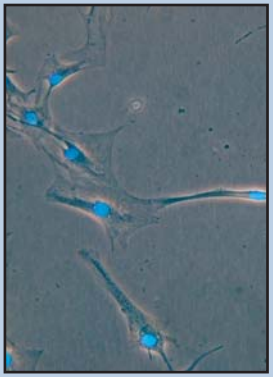
>> First and only described technique that enables the obtention of platelets exclusively; excluding leukocytes eliminates inflammatory interleukines of leukocytal origin.

>> The system and protocol is simple, user-friendly and affordable.

** "Some of the products present in this brochure are not available for distribution in the USA, yet".

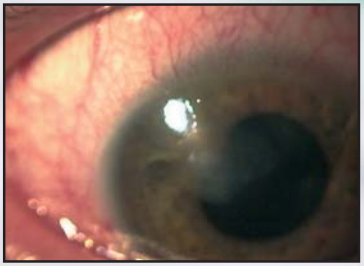
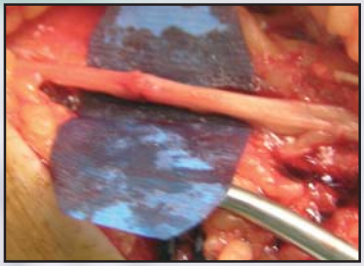





PRGF: clinical applications in various medical areas



>> PRGF technology opens new perspectives in the area of **human tissue regeneration and is a valuable tool to treat a wide range of tissue injuries.**

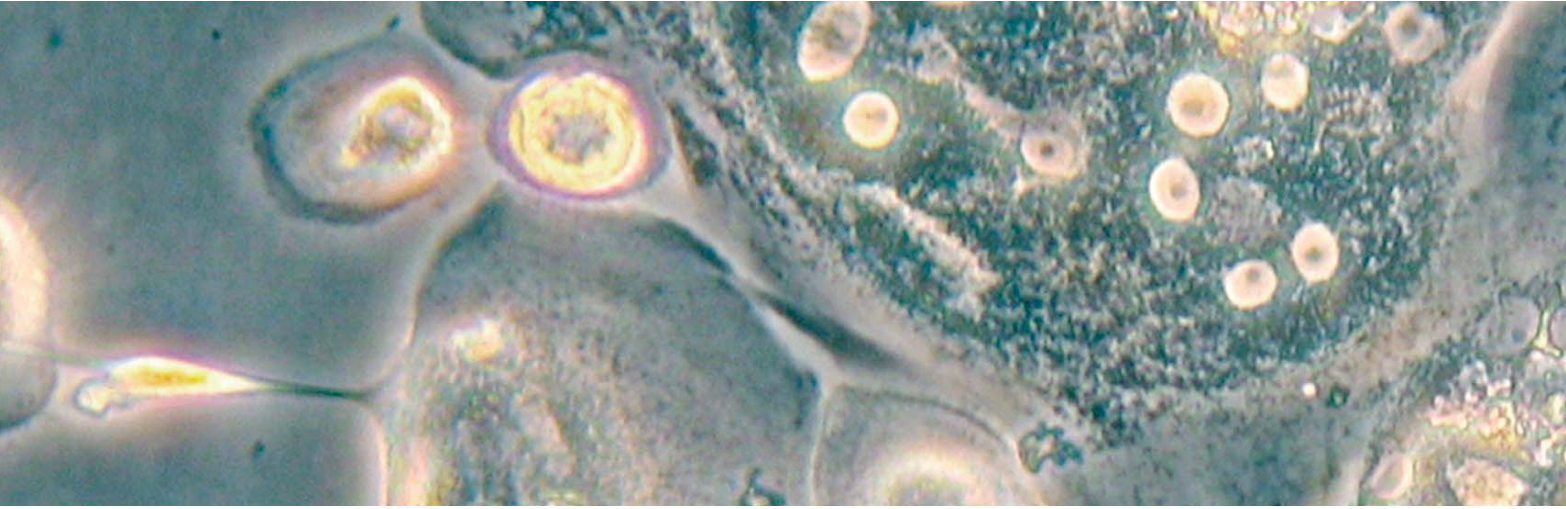


>> Medicine is continually adopting novel therapies and less invasive procedures that reduce morbidity and enhance functional recovery while reducing costs. The practice of surgery has been affected by the emergence of PRGF which have opened new avenues for therapeutic approaches because of its accessibility and repair capacity.

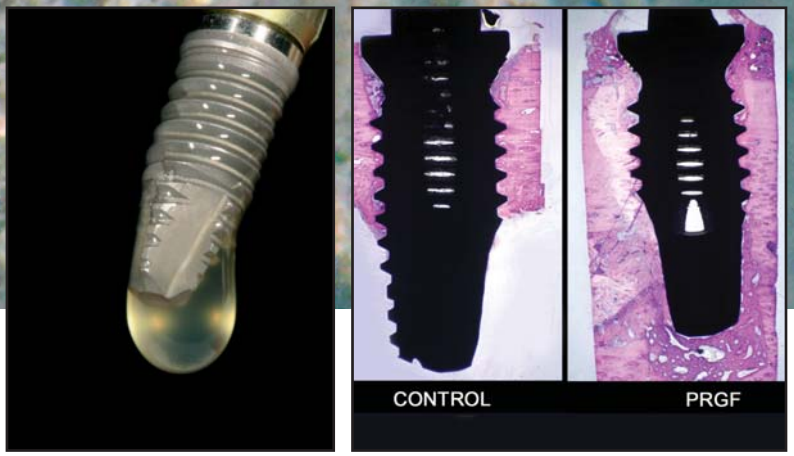
PRGF is a cocktail of native proteins obtained from a convenient, autologous source such as blood that adjust the supply of signalling molecules to the specific needs of the injured tissue. Considerable research and clinical efforts are being made to develop novel PRGF procedures aiming to improve the therapeutic treatments for a wide range of clinical conditions.

PRGF technology has opened new therapeutic possibilities in diverse medical areas such as **Orthopaedics, Arthroscopic Surgery Sports Medicine, Dentistry, Maxillofacial Surgery, Periodontal Surgery, Aesthetic Medicine, Ulcer treatment, Ophthalmology and Peripheral Nerve Repair.**



Oral Surgery applications

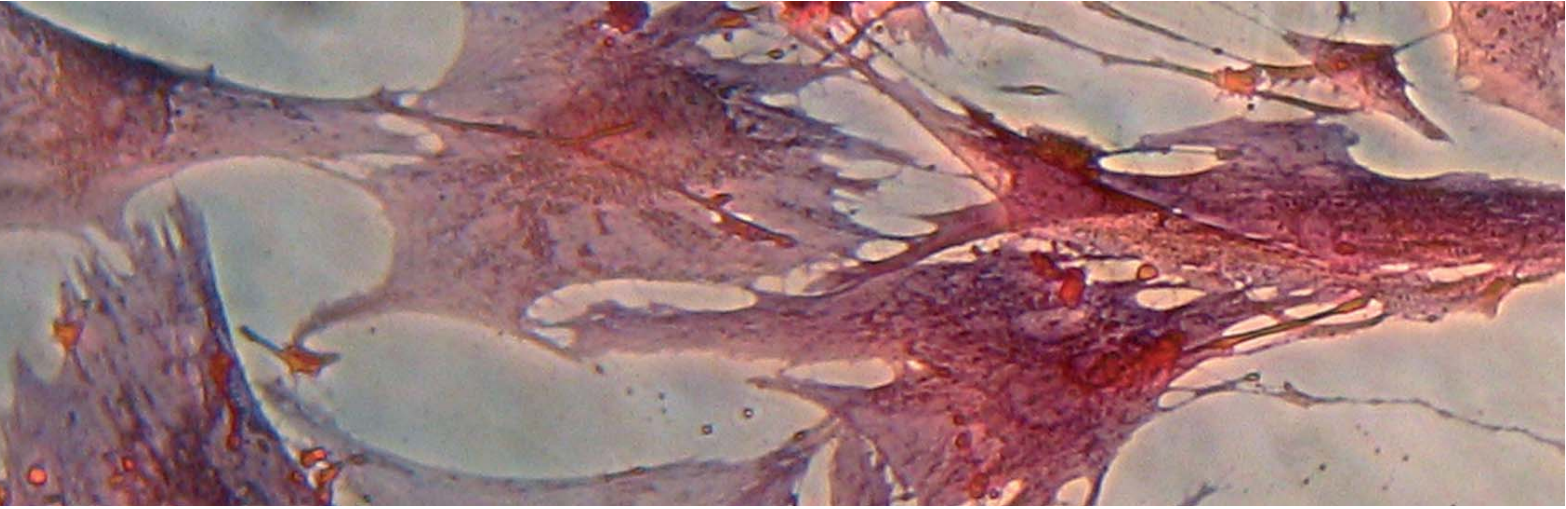
>> BIOACTIVATING THE IMPLANT SURFACE



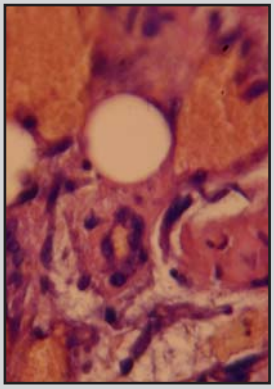
Experimentally proven effectiveness. After 8 weeks, a 134% BIC (bone-implant contact) increase was observed.

>> Combination of PRGF with dental implants facilitates the anchorage of dental prostheses: PRGF when applied to humidify BTI dental implants adheres to the pre-conditioned titanium surface improving the osteogenic properties of the implants by creating a new dynamic surface with biological activity.

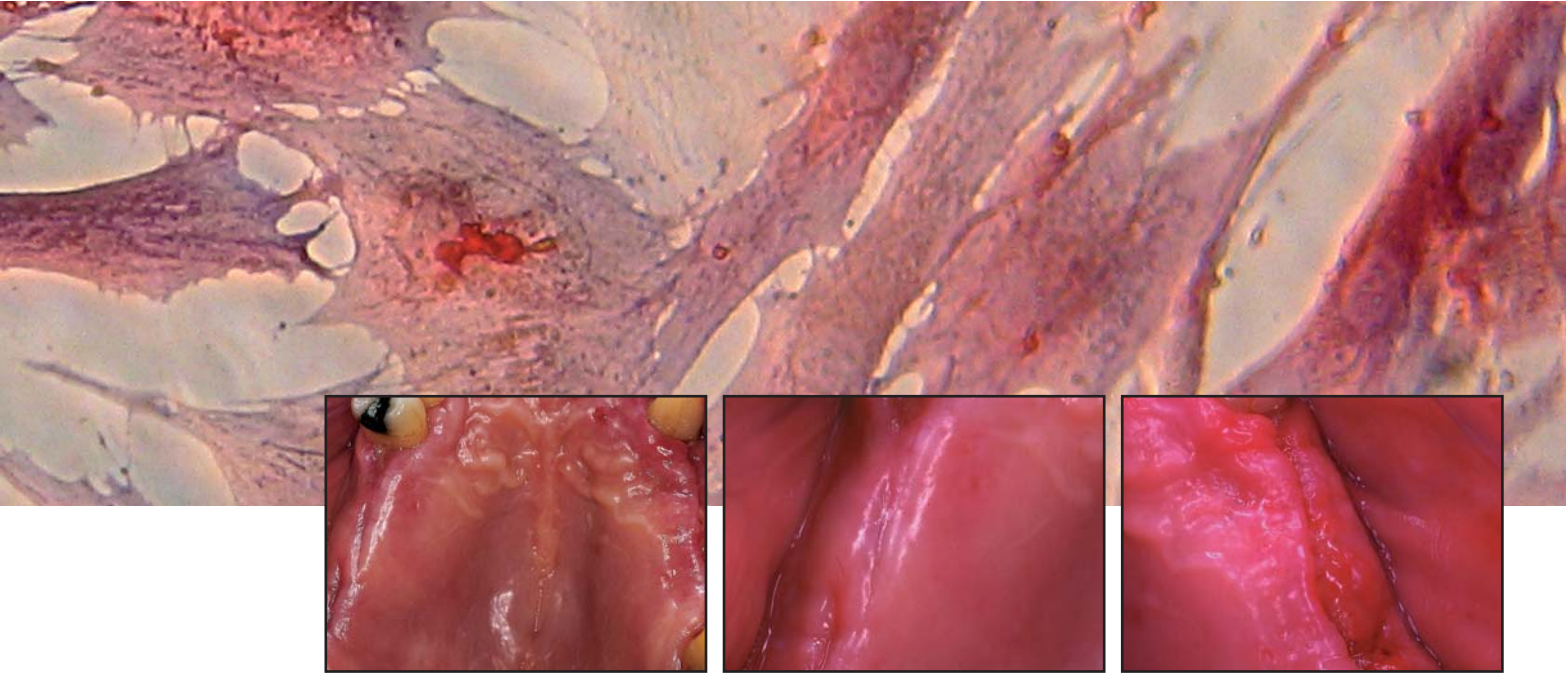
PRGF-bioactive surface improves the integration of oral titanium implants in trabecular bone and has major implications in obtaining a suitable implant osseointegration and consequently high implant stability.



Oral Surgery applications



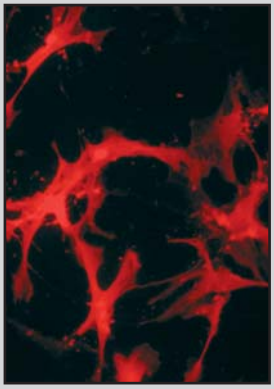
>> IMPROVES EPITHELIALIZATION



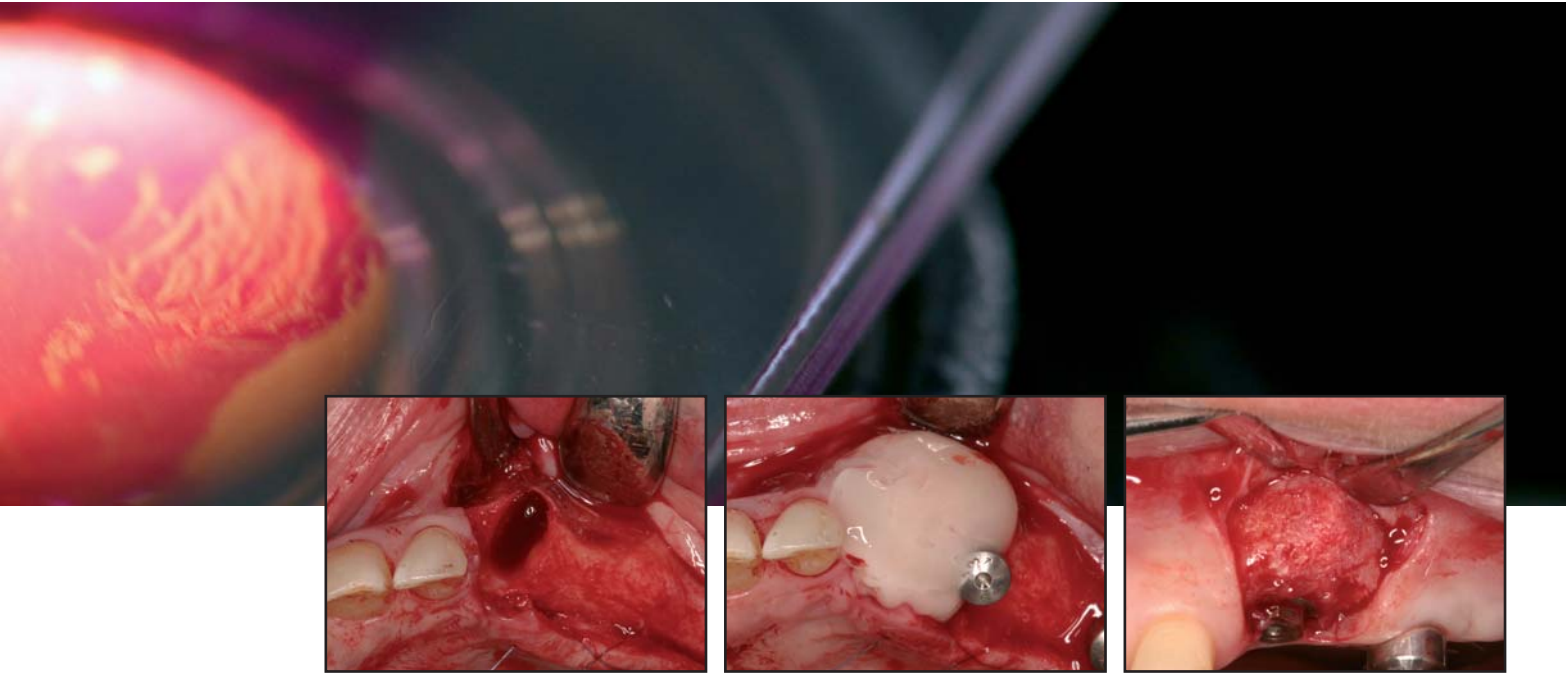
There is a remarkable difference between the side treated with PRGF and the control zone.

>> 54-year old patient with implants placed in both hemiarches; in the photos we can see the epithelialization after 4 days. On the left side, PRGF was used; the right side was used as the control zone.

Oral Surgery applications



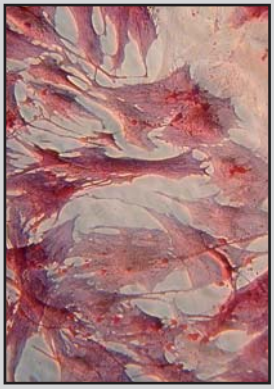
>> TREATMENT OF EXTRACTION SITE



>> Alveolar bone regeneration will be more straightaway after a single tooth extraction. Filling the extraction site with PRGF is done in the same surgery as the extraction. To do so the recently coagulated PRGF is introduced into the alveolus and the sealing is done with autologous fibrin, prepared through PRGF technology. PRGF-fibrin possesses excellent elastic and hemostatic properties.

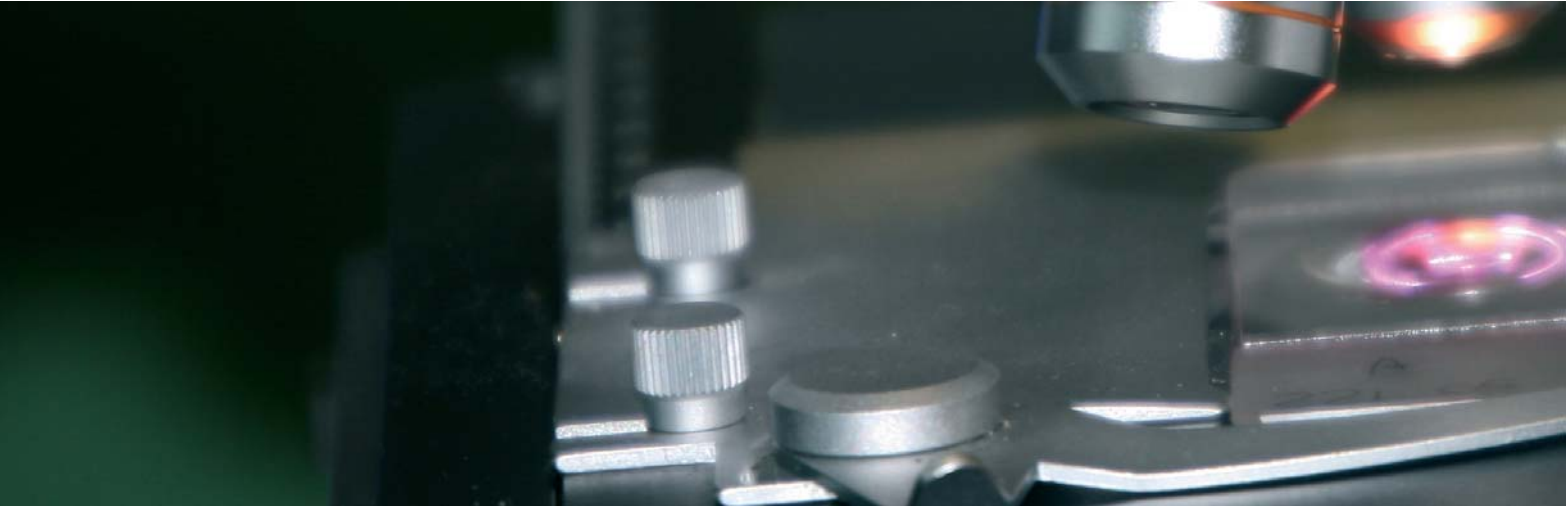
This procedure overcomes the placement of split thickness flaps to assure primary closure of the alveolus.

Oral Surgery applications

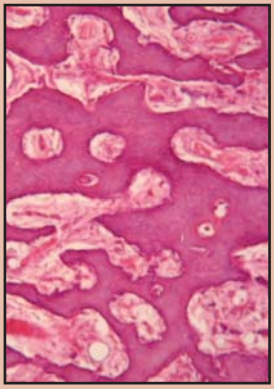


>> BONE DEFECTS AROUND IMPLANTS - ***graft handling***

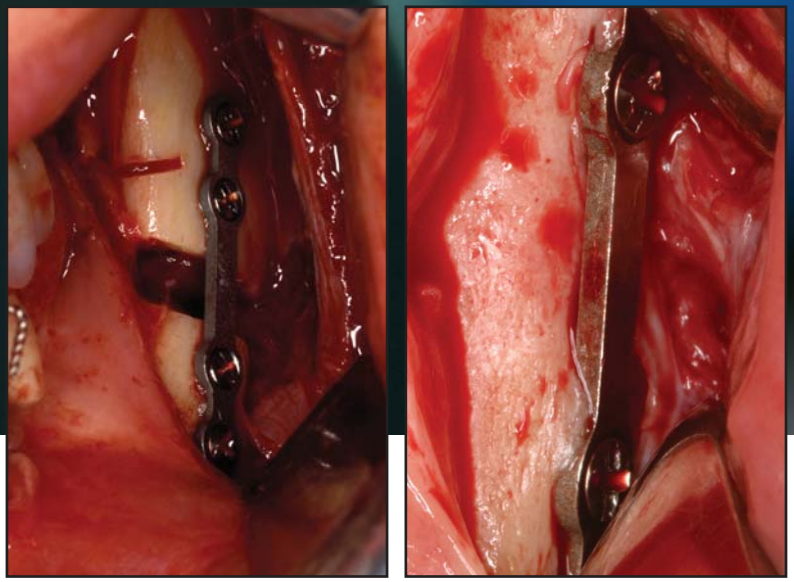
>> Periodontal defects show precise histological features. First of all the root surface is not osseoconductive and both osseous tissue an periodontal ligament should be restored. Moreover the graft will be exposed thus encompass a higher risk of contamination.



Maxillofacial Surgery applications



>> MAXILLOFACIAL SURGERY



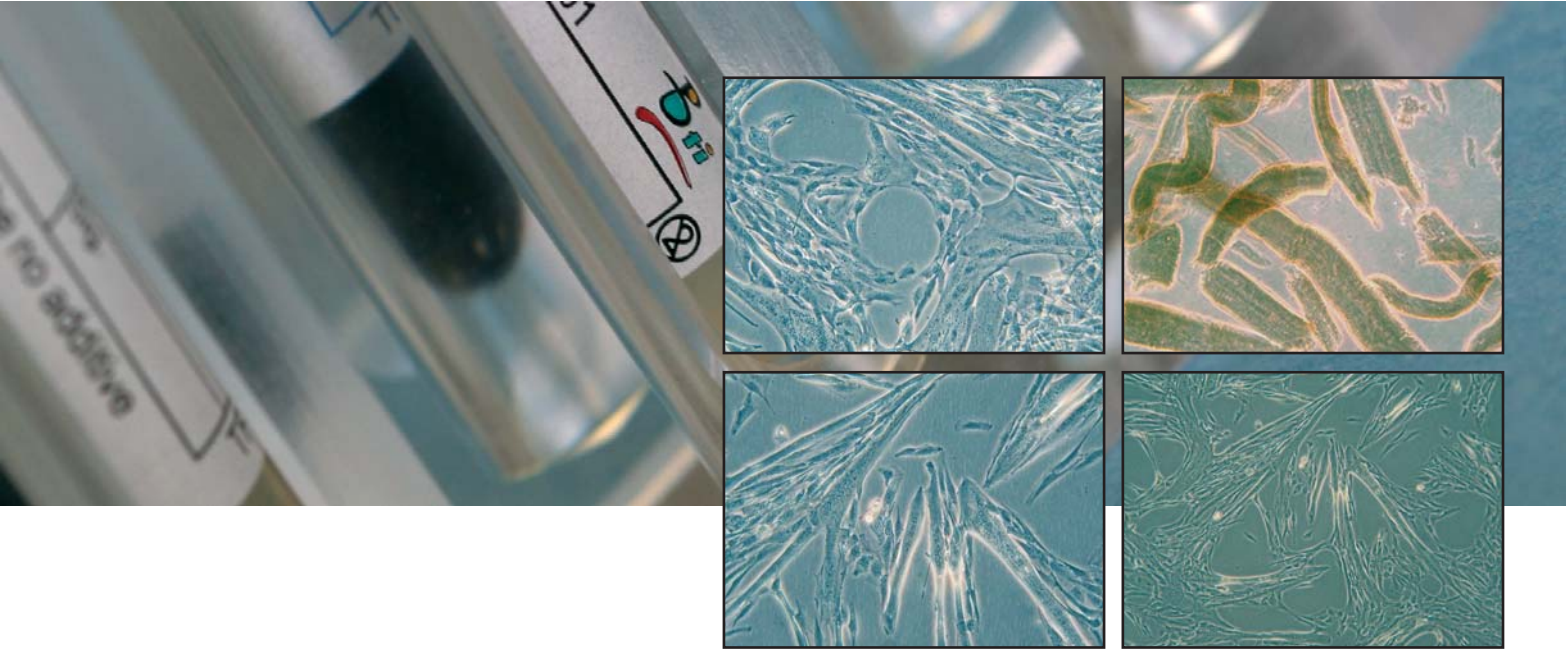
After re-opening, the osteotomy is perfectly consolidated.

>> PRGF application during the reconstruction of mandibular continuity defects results in a significantly faster maturation and denser bone regeneration. The resulting bone tissue is compact with well-organized trabeculae.

PRGF enhances bone regeneration due to its specific properties, some of which include its biocompatibility, biodegradability, easy preparation and manipulation, versatility, osteoinductive properties due to the growth factors released and osteoconductive properties due to the fibrin scaffold.

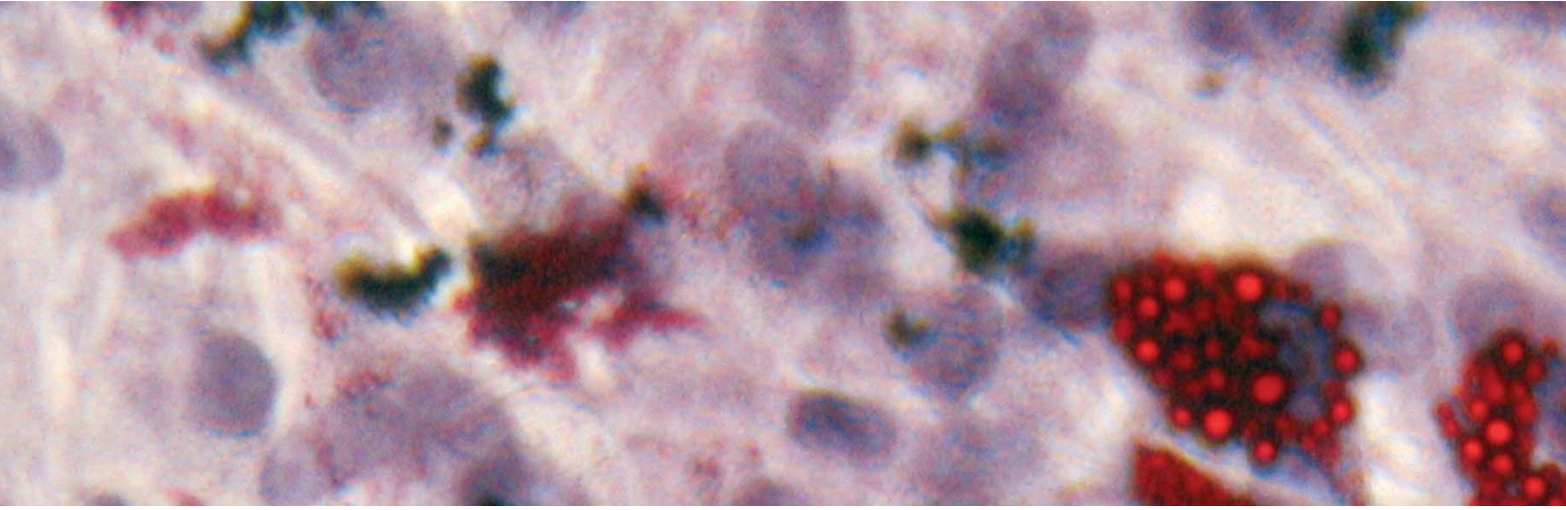
Sports Medicine

>> MUSCLE INJURIES

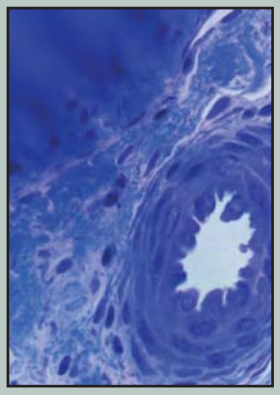


>> Ultrasound guided injection of PRGF within the injured muscle enhances healing and thereby functional recovery.

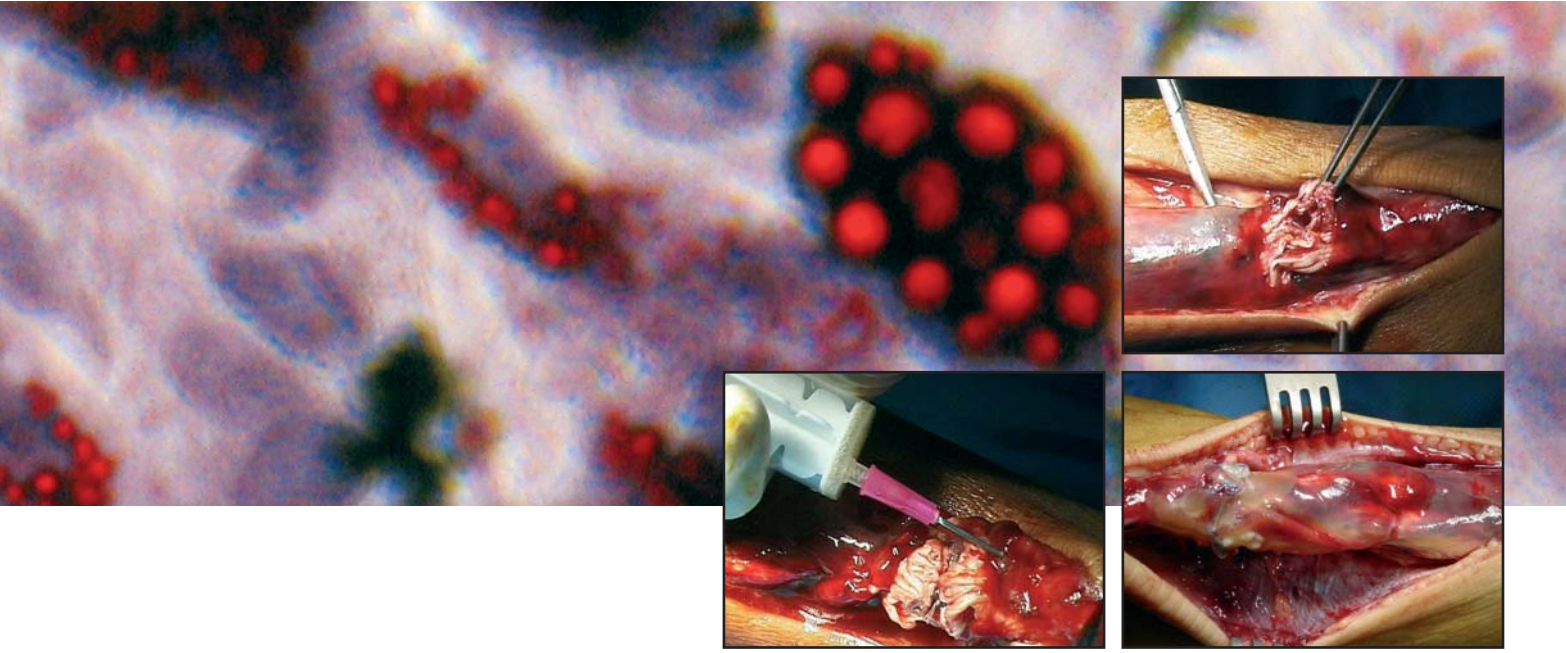
In a multicenter study PRGF treatment diminished swelling, and reduced pain. Full recovery of functional capability was achieved as early as half of the expected recovery times and no re-injuries occurred in any athlete after resuming their normal sports activities.



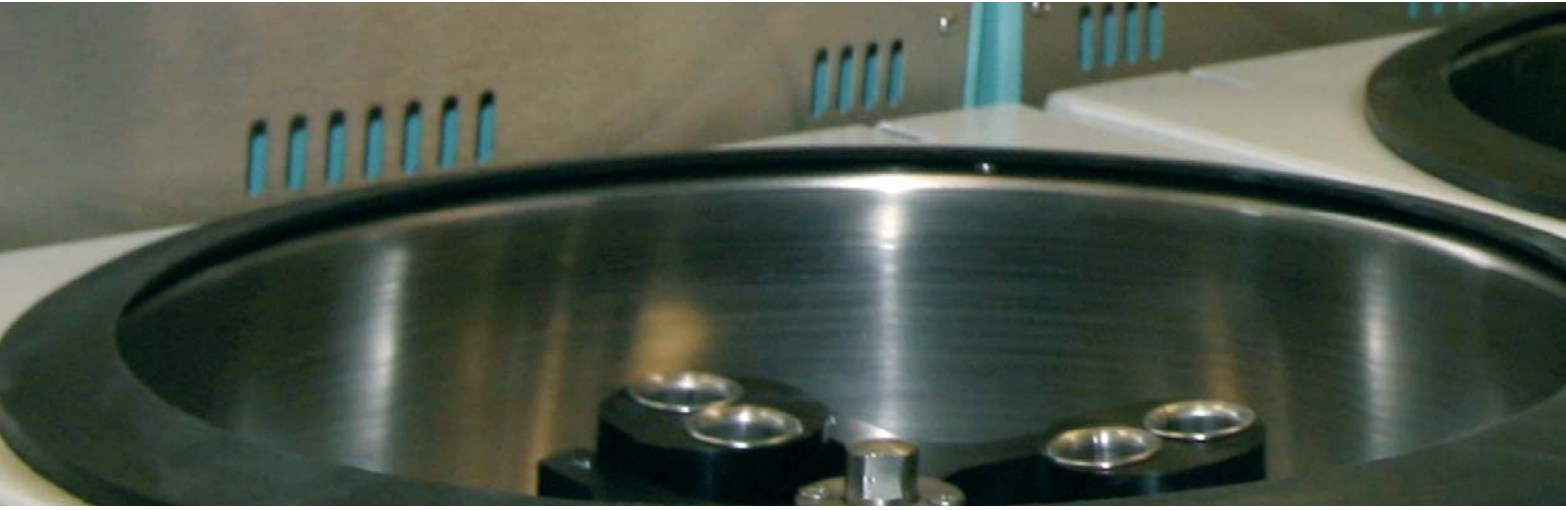
Sports Medicine



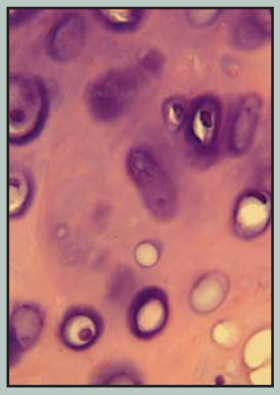
>> TENDON INJURIES



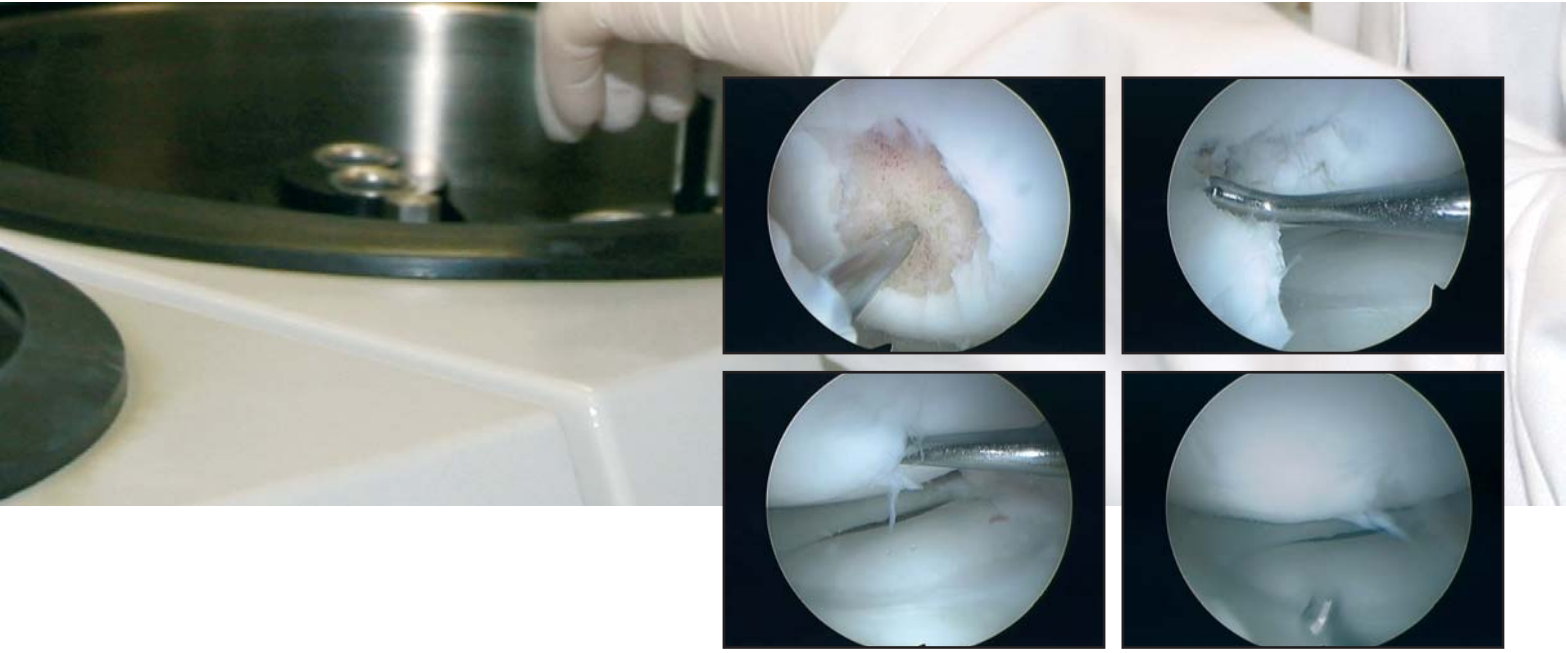
>> Soft-tissue disorders including tendon, ligament and joint capsular injuries represent 45% of all the musculoskeletal injuries reported each year in the US, with a high incidence among sports practitioners. It is now estimated that tendon injuries account for between 30 and 50% of all injuries related to sports and these often require surgical treatment. In these situations, application of PRGF together with the surgical procedure may enable the surgeons to enhance and accelerate reconstruction and repair of musculoskeletal tissues affording new opportunities for improving the outcome and reducing the costs. PRGF applied during open surgical repair of Achilles tendon in athletes showed an enhanced clinical outcome and functional recovery.



Arthroscopic Surgery

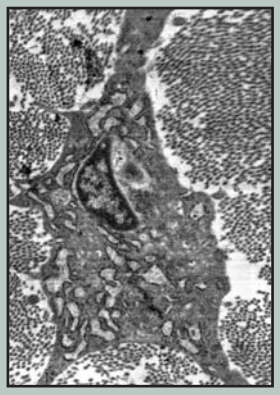


>> CHONDRAL INJURIES

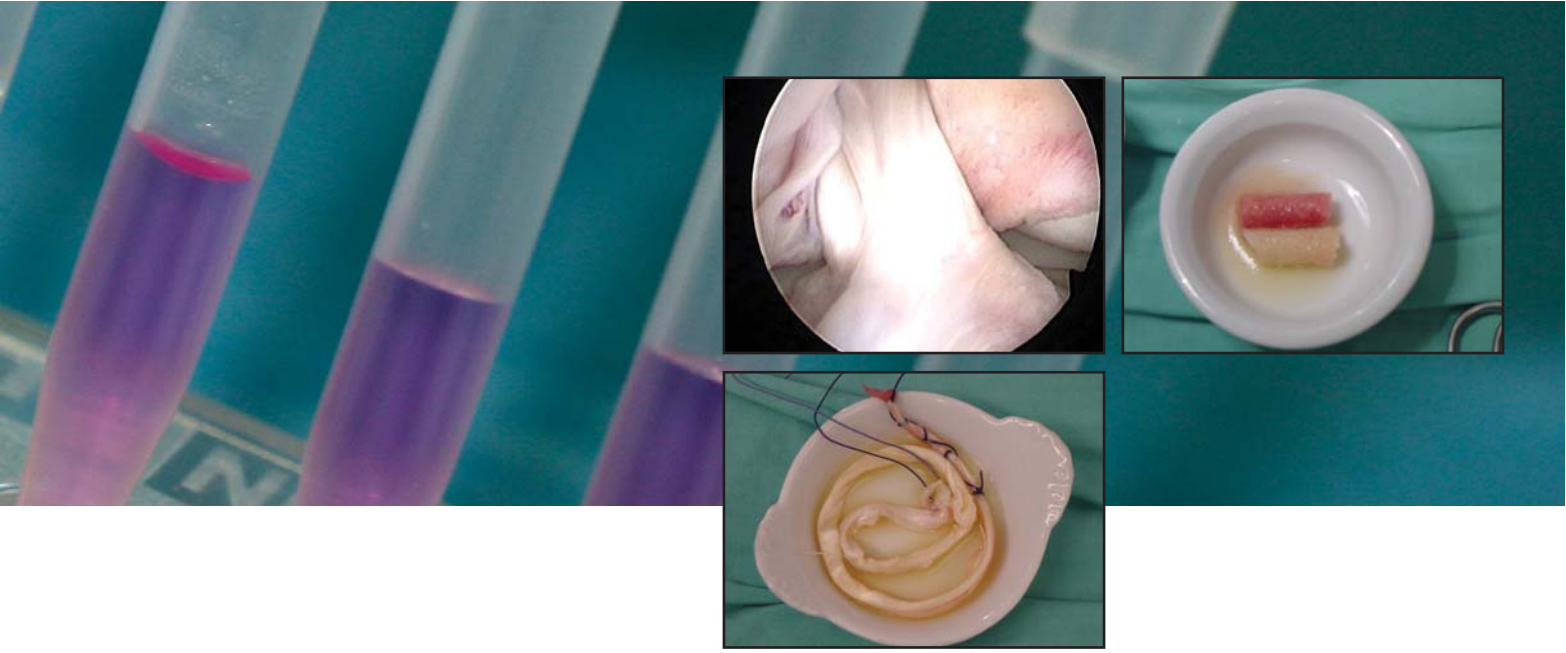


>> Articular cartilage is vulnerable to injury and has poor potential for repair. The problem is very serious in sports medicine, particularly inherent to professional athletes which after injury must be functionally recovered in the shortest period. PRGF applied during arthroscopic surgery contribute to the accelerated cartilage regeneration in part due to some of the key factors released to the local medium which are known to play pivotal roles in the biological activities of the chondrocytes.

Arthroscopic Surgery



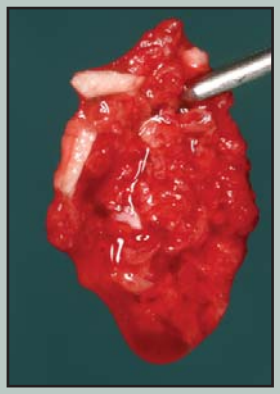
>> ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION



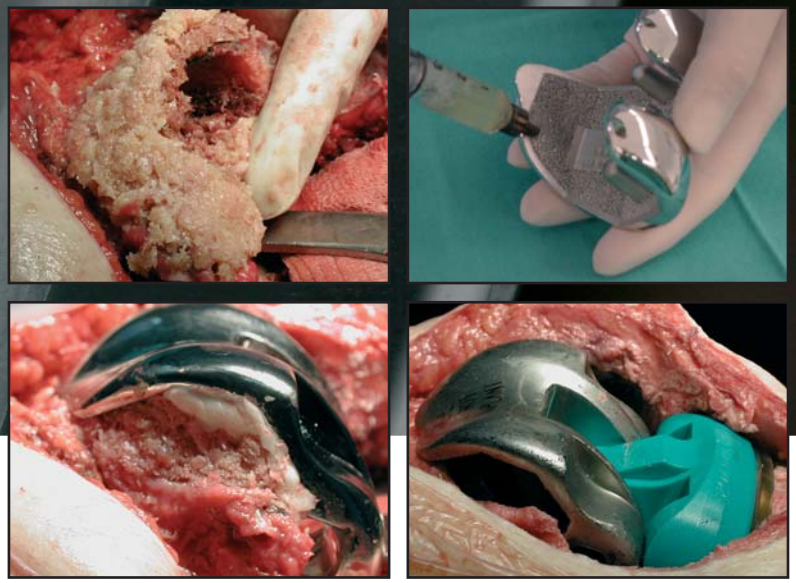
>> In the anterior cruciate ligament (ACL) surgery the injured ligament is removed by arthrocopic surgery and the joint is reconstructed with a tendon graft in which PRGF has been injected. ACL reconstruction also involves creating a tunnel through the tibia, drilling a closed tunnel into the femur and inserting a substitute graft from one tunnel to the other. By providing PRGF within the tibial tunnel and applying it into the femoral socket it is possible to accelerate bone growth and enhance fixation of the graft.

In all of these situations in which patients are obligated to wait long periods of time, the use of PRGF might be very useful to accelerate tissue regeneration and function

Orthopaedic Surgery



>> PROSTHETIC SURGERY

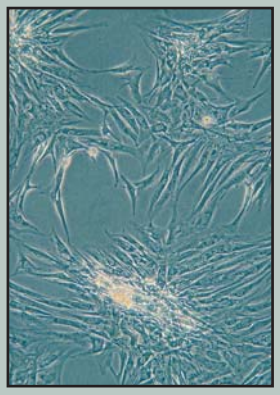


>> PRGF is a clinically safe graft enhancer showing a high rate of success when used in combination ith either bone autografts or allografts.

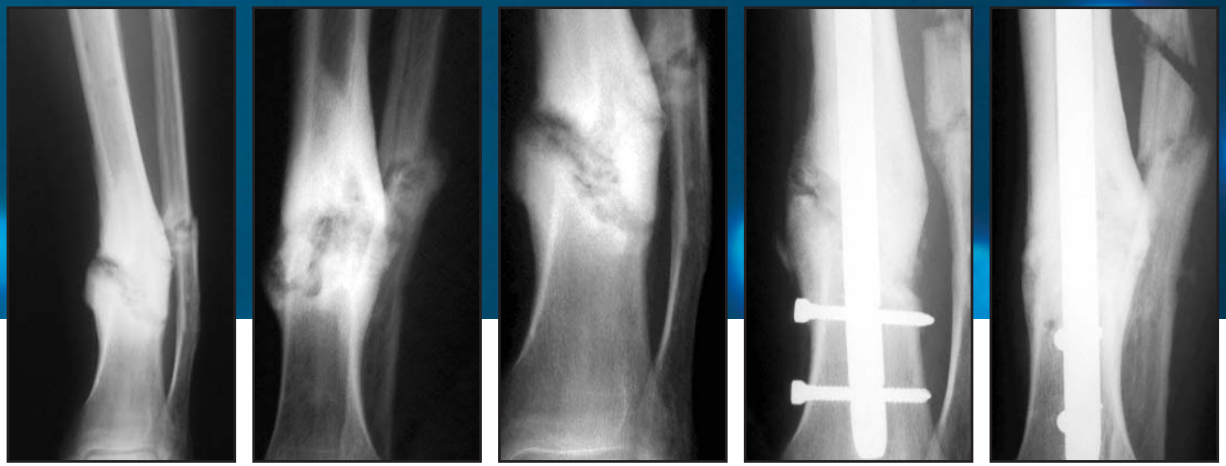
After activation with calcium chloride and combination with morselized bone, a 3-D fibrin scaffold develops agglutinating the graft particles rendering a handily product easy to manipulate during surgery and adapt to the injured site.

PRGF improves the integration of prosthetic devices in trabecular bone and has major implications in obtaining a suitable osseointegration and consequently high stability.

Orthopaedic Surgery

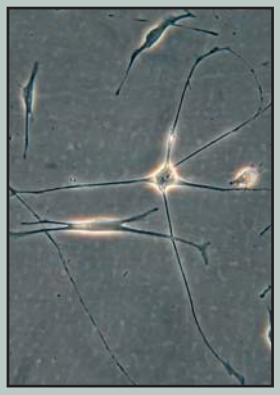


>> NONUNIONS OF LONG BONES



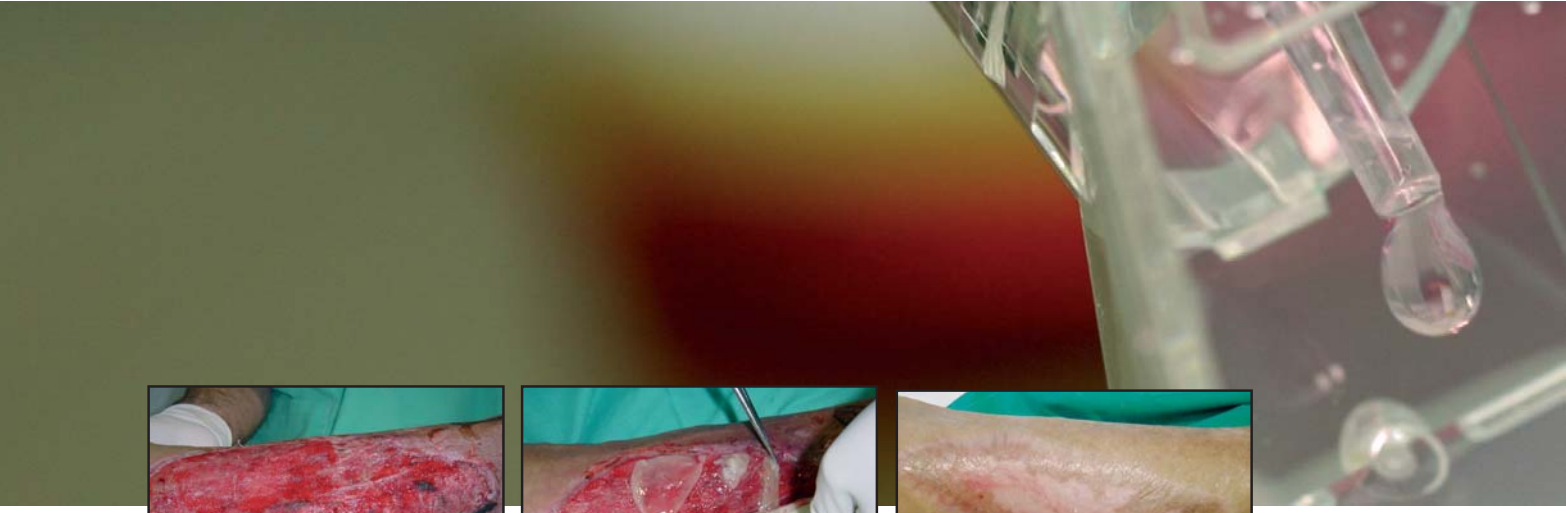
>> Nonunion of fracture occurs when the normal biologic healing processes of bone ceases, so that solid healing will not achieve without further treatment. Application of combined grafts consisting of either autologous or homologous bone mixed with PRGF enhanced bone healing and after 5-8 months all treated patient showed clinical and radiographic signs of complete fracture healing.

PRGF treatments

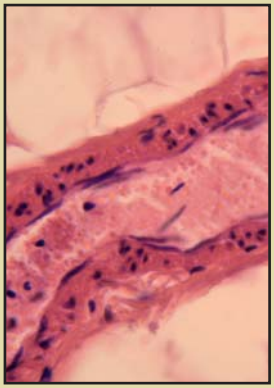


>> INFILTRATIONS

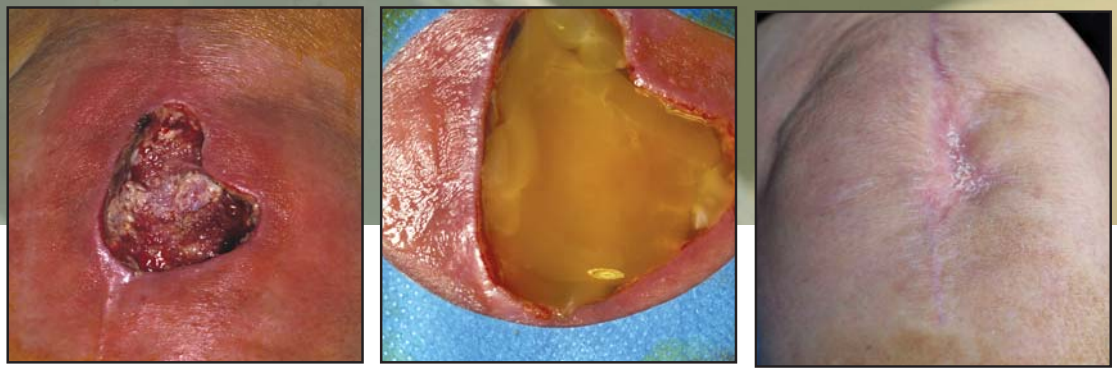
>> Dysregulated growth factor signalling may cause the pathogenesis of many degenerative changes and one way to drive these tissues back to homeostasis is to manipulate cell signalling by infiltrating a highly biocompatible Preparation Rich in Growth Factors.



PRGF treatments

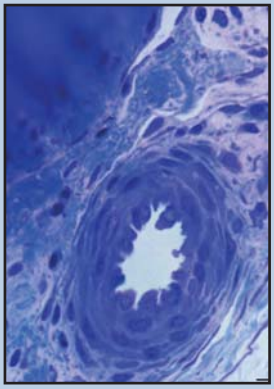


>> ULCER TREATMENT

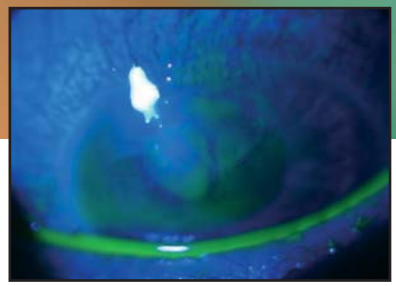


>> Ulceration of the lower limbs is a common complication of a wide spectrum of pathologies that cause a negative impact on the quality of life of the affected patients. Clinical data strongly support safety and effectiveness of PRGF formulation as a therapeutic treatment for accelerating the healing process of different chronic ulcers in a reduce period of time.

PRGF treatments



>> OPHTHALMOLOGY

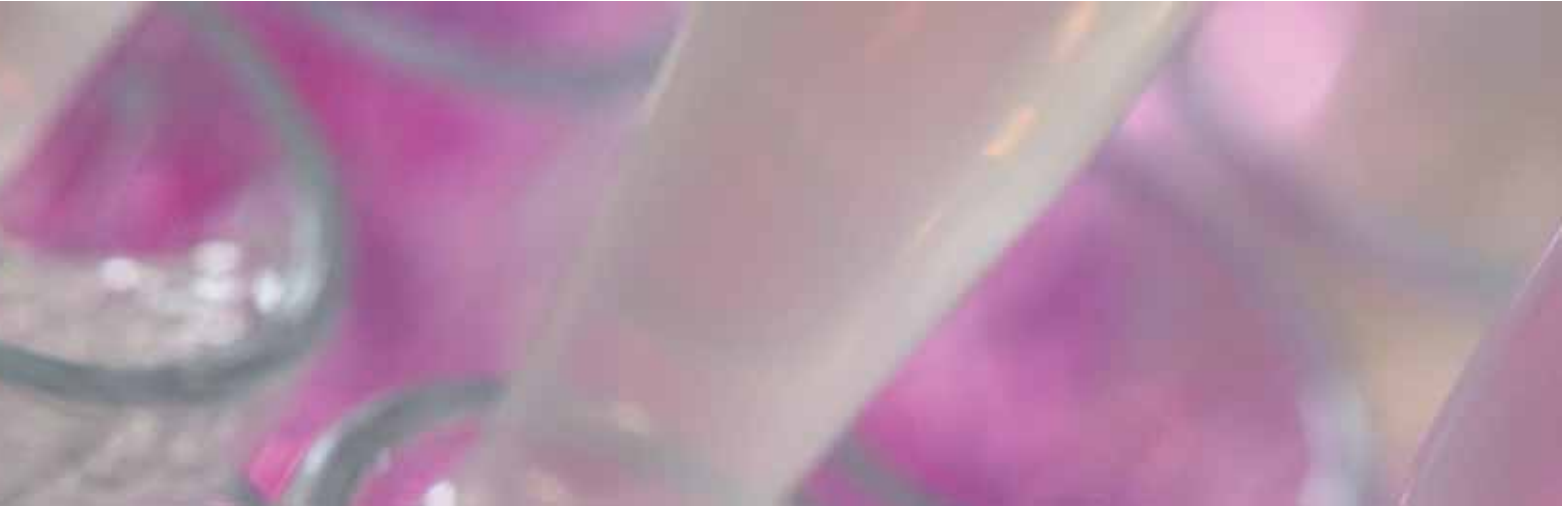


>> Corneal dormant ulcers: PRGF can be applied either topically, eye drops prepared by means of PRGF technology or surgically as a PRGF-clot. In both procedures of application PRGF has been shown to be a reliable and efficient procedure to restore the corneal epithelial surface.

Research & Development BTI®

In the last decade, Biotechnology Institute (BTI®) has made much effort towards the scientific development and optimization of its products, mainly with the aim of ensuring their efficacy and biosafety. As a consequence, BTI® has successfully developed and applied the technology of PRGF in a wide range of situations and clinical disorders. Additionally, we have produced dental implants characterized by a great cutting capacity apex design and by a micro-rough acid-etched surface which facilitates implant osseointegration, minimizing compression and host bone damage. Last but not least, we have developed different clinical and surgical protocols that have opened new avenues for example in dentistry and oral implantology and in the treatment of several musculoskeletal disorders.

The research publications summarized in this BTI® scientific dossier illustrates the enormous efforts made in Research and Development during the last few years. This dossier is divided into four general sections:



PRGF: Pre-clinic research

Characterization, cell culture and animal experimental research

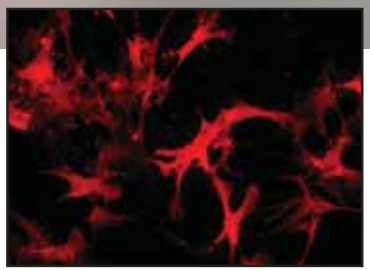
PRGF: Therapeutic applications in different medical fi

Oral implantology, sports medicine, traumatology, vascular medicine, rheumatology

Dental implants BTI®

Surface modifications, biomechanics, dental implant survival

Innovation of protocols and surgical techniques

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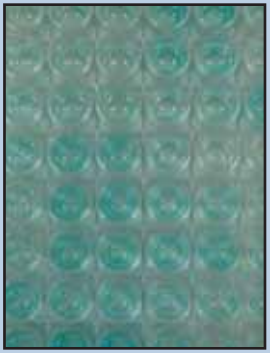
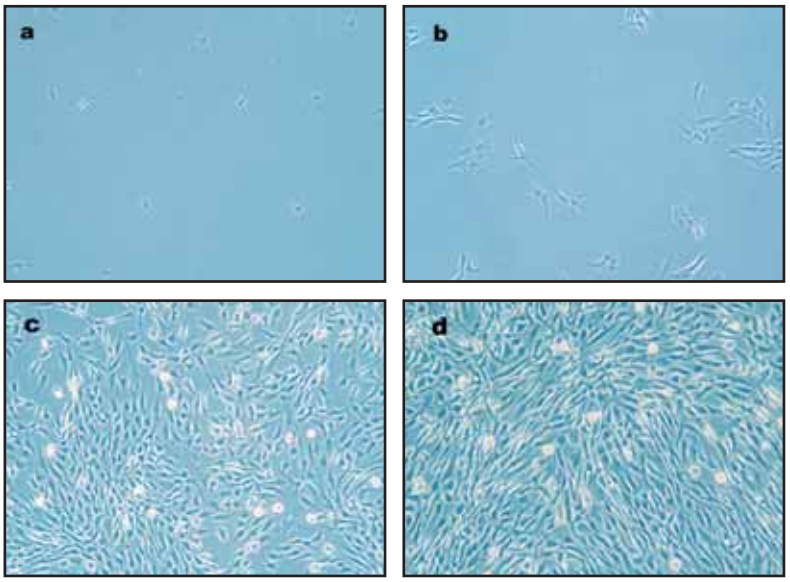
PRGF: Pre-clinic research

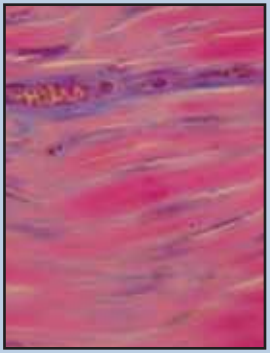


Anitua E, Andía I, Sanchez M, Azofra J, Zalduendo M, Maria de la Fuente, Paquita Nurden, Alan T Nurden. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. J Orthop Res 2005;23:281-286.

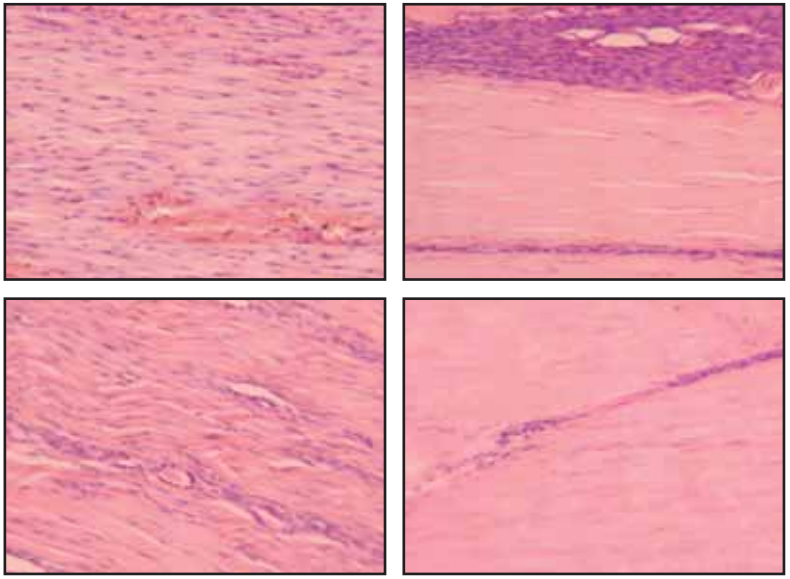


Blood platelets become activated and aggregate at the site of vessel injury. Upon activation by thrombin, platelets release storage pools of proteins and growth factors (GFs), including those involved in tissue repair. In the present work we have evaluated the potential beneficial effects of proteins released from platelet-rich clots on tendon healing. We have studied the effects of the pool of factors released from either platelet-poor or platelet-rich fibrin matrices from four different donors on human tendon cells in culture. Our results showed that the molecules released from both platelet-rich and platelet-poor clots stimulated tendon cell proliferation, in contrast to unclotted PPP. The mitogenic activity of the supernatants was only partially decreased by the thrombin inhibitor, hirudin. In addition tendon cells synthesised higher amount of HGF and VEGF when stimulated by platelet secreted factors. These results indicate that the administration of autologous platelet-rich clots may be beneficial to the treatment of tendon injuries by inducing cell proliferation and promoting the synthesis of angiogenic factors during the healing process.

PRGF: Pre-clinic research

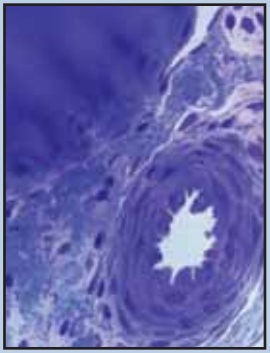


Anitua E, Sanchez M, Nurden AT, Zalduendo M, de la Fuente M, Orive G, Azofra J, Andia I. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. J Biomed Mat Res 2006;77:285-293.

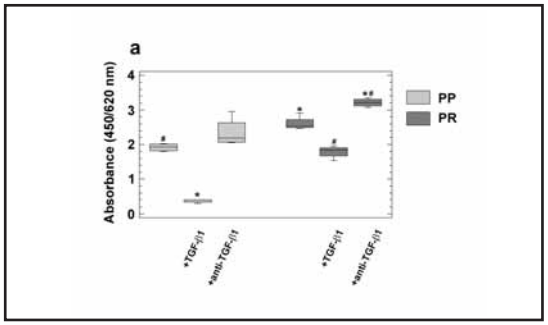


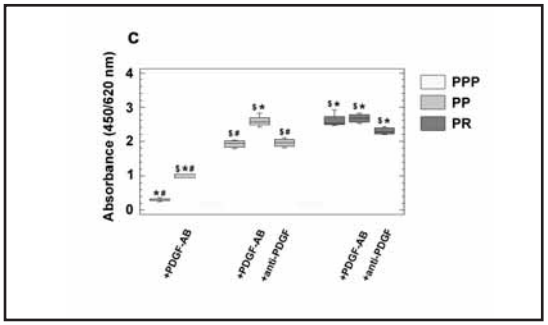
In this paper we propose the use of autologous fibrin matrices as a therapeutic strategy for the local and physiological delivery of growth factors in the treatment of several clinical conditions requiring tendon healing or tendon graft remodeling. Thus we examined the proliferation, synthesis of type-I collagen and angiogenic factors by tendon cells seeded on platelet rich (PR) and platelet poor (PP) matrices. Furthermore, were examined the in vivo cellular and vascular effects of each treatment after infiltration in Achilles tendon in sheep. Our results showed that the presence of platelets within the fibrin matrices increased significantly the proliferation of tendon cells. Additionally, cultured tendon cells synthesized type I collagen and angiogenic factors such as VEGF and HGF. The synthesis of VEGF, but not of HGF, was significantly higher when platelets were present within the matrix. In the sheep model, the injection of pre-clotted plasma within tendons increased cellular density and promoted neovascularization. These results indicate that administration of fibrin matrices is a safe and easy strategy that may open new avenues for enhancing tissue healing and remodeling and influence the process of regeneration in clinical situations characterized by a poor healing outcome.

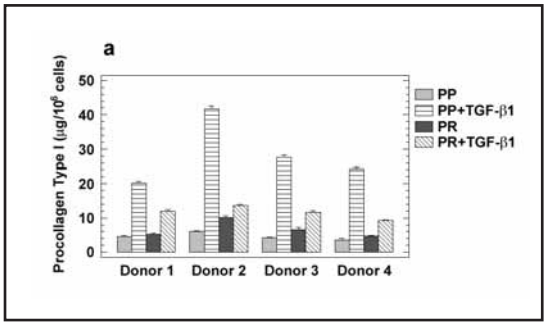
PRGF: Pre-clinic research



Anitua E, Sanchez M, Nurden AT, Zalduendo M, de la Fuente M, Azofra J, Andia I
Reciprocal actions of platelet-secreted TGF-ß1 on the production of VEGF and HGF by human tendon cells. Plastic Reconstruct Surg 2007;119:959-959.

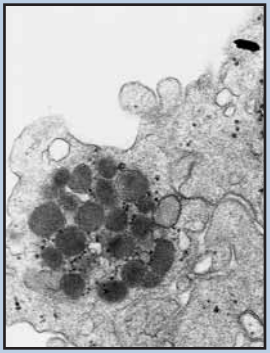






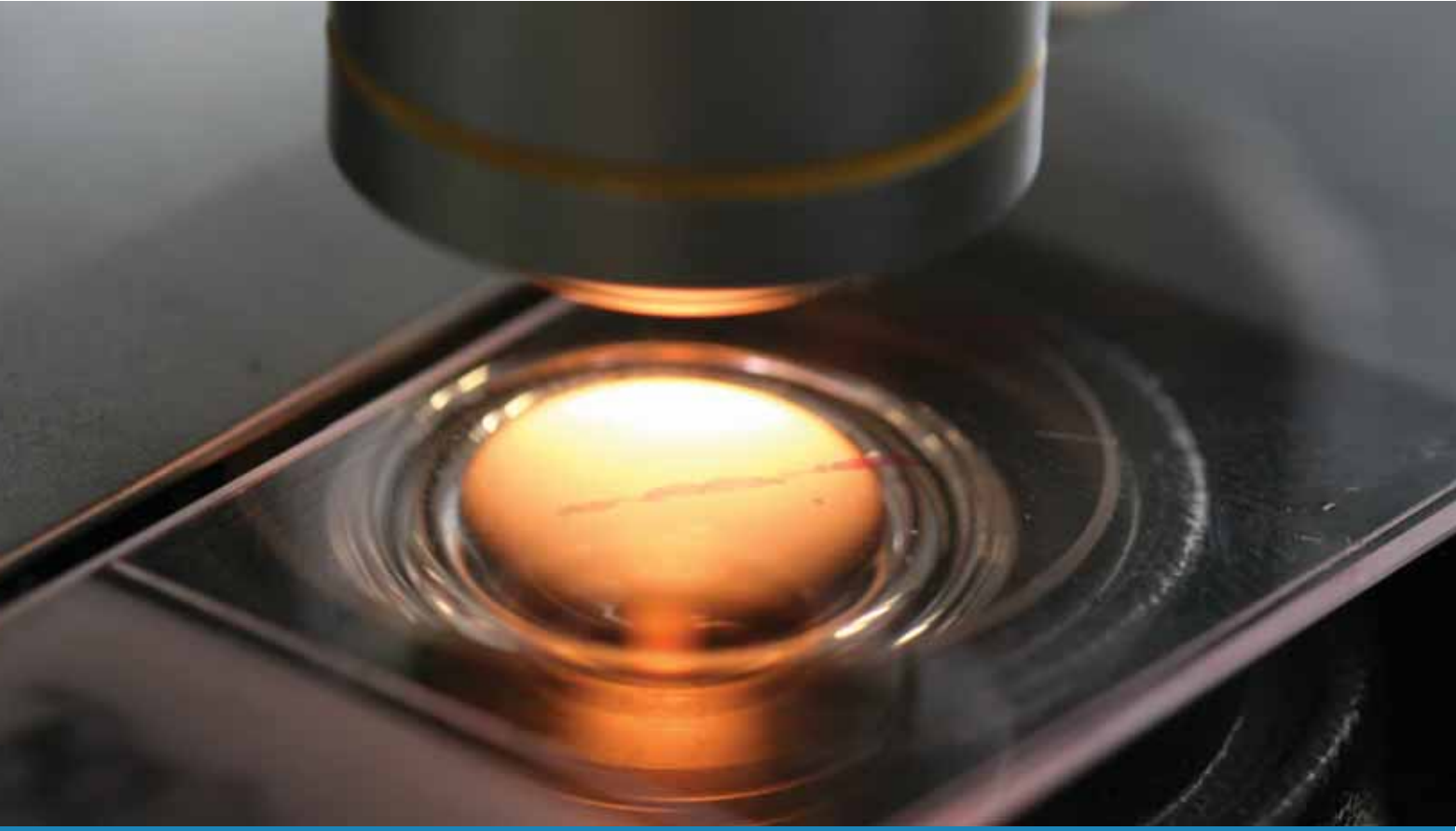
Autologous platelet-rich matrices can be an aid in surgery by promoting and accelerating tissue healing. In the present work we aimed to evaluate the potential role of the most abundant platelet secreted growth factors, transforming growth factor (TGF-ß1) and platelet-derived growth factor (PDGF), in tendon repair. Therefore we studied human tenocyte proliferation and maturation after exposing cells in culture to treatments differing by the presence or the lack of the bulk of platelet-secreted molecules. In the presence of the total pool of platelet-secreted molecules PDGF was a partial contributor to cell proliferation while exogenous TGF-ß1 acted as a negative modulator. The production of type I collagen was similar regardless of differences in the concentration of TGF-ß1. Moreover, addition of exogenous TGF-ß1 promoted a significant increase in collagen synthesis only in the absence of other platelet released substances. Interestingly, exogenous TGF-ß1 increased the synthesis of vascular endothelial growth factor (VEGF) and simultaneously abolished the production of hepatocyte growth factor (HGF). Furthermore, antibody-mediated neutralization of TGF-ß1 induced a decrease in VEGF synthesis and concomitantly a substantial production of HGF. All these data demonstrate that the balance between TGF-ß1 and the pools of platelet-secreted molecules may have important therapeutic implications in the control of angiogenesis and fibrosis.

PRGF: Pre-clinic research



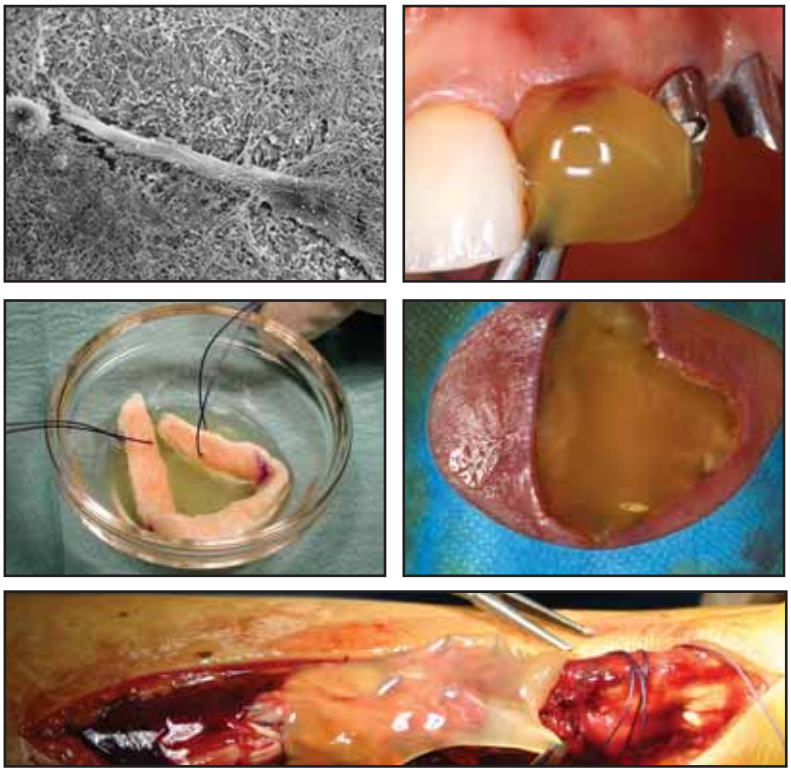
Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 2004;91:4-15.

Platelets are primarily known for their role in haemostasis, where they help prevent blood loss at sites of vascular injury. To do this, they adhere, aggregate and form a procoagulant surface leading to thrombin generation and fibrin formation. Platelets also release substances that promote tissue repair and influence the reactivity of vascular and other blood cells in inflammation and angiogenesis. Thus they contain storage pools of growth factors including PDGF, TGF-ß and VEGF as well as cytokines and proteins such as PF4 and CD40L. Chemokines and newly synthesised active metabolites are also released. The fact that platelets secrete growth factors and active metabolites means that their applied use can have a positive influence in clinical situations requiring rapid healing and tissue regeneration. Their administration in fibrin clot or fibrin glue provides an adhesive support that can confine secretion to a chosen site. Additionally, the presentation of growth factors attached to platelets and/or fibrin may result in enhanced activity over recombinant proteins. Dental implant surgery with guided bone regeneration is one situation where an autologous platelet-rich clot clearly accelerates ossification after tooth extraction and/or around titanium implants. The end result is both marked reductions in the time required for implant stabilisation and an improved success rate. Muscle and/or tendon repair in sports medicine, skin regeneration and skin ulcers, hole repair in eye surgery and facial plastic surgery are other situations where autologous platelets accelerate healing. In this work we reviewed these advances and briefly discussed the ways in which platelets may provide such unexpected beneficial therapeutic effects.



PRGF: Pre-clinic research

Anitua E, Sánchez M, Nurden AT, Nurden P, Orive G, Andía I. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol 2006;5:227-234.



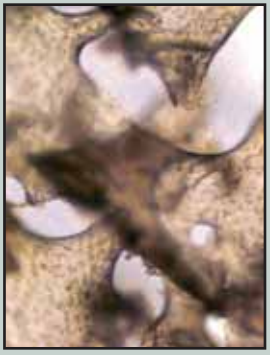
This is the highest impact factor research article describing the properties of platelet rich products and specifically the PRGF (preparation rich in growth factors). This is a relatively new biotechnology that has been a breakthrough in the stimulation and acceleration of soft tissue healing and bone. This is in part because PRGF allows the local and continuous delivery of a wide range of growth factors and proteins, mimicking the needs of the physiological wound healing and reparative tissue processes. As a consequence, the application of platelet rich plasma and more specifically PRGF has been extended to many different fields including dentistry, oral implantology, orthopedics, sports medicine, cosmetic, wound healing and oral and maxillofacial surgery. This article highlights the use of this technology and discusses some of the obstacles and challenges that need to be addressed to maintain progress in this field.

PRGF: Pre-clinic research

Anitua E, Sánchez M, Nurden AT, Zalduendo M, de la Fuente M, Azofra J, Andia I. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Submitted 2007.

Autologous growth factors may have therapeutic effects in OA capsular joints via multiple mechanisms. In this study we have focused on synovial biology and examined the effect of PRGF in several events relevant to joint homeostasis including (i) hyaluronic acid (HA) secretion, (ii) the balance between metalloproteinase-1, -3 and -13 (MMP-1, MMP-3 and MMP-13) and tissue inhibitor-1 (TIMP-1), and (iii) the secretion of pro-angiogenic factors. Synovial cells, isolated from 10 osteoathritic patients with severe osteoarthrosis, were stimulated or not with interleukin-1ß and then exposed to PRGF Our data showed that PRGF enhanced the basal secretion of HA by synovial fibroblasts; but did not modify the catabolic status induced by IL-1ß. An increased HGF production was observed but VEGF and TGF-ß1 levels remained unchanged. PRGF did not modify the IL-1ß induced rise in VEGF but significantly reduced HGF production. Intra-articular administration of PRGF might be beneficial in restoring HA levels within the joint and switching angiogenesis to a more balanced status but does not halt the effects of IL-1ß on synovial cells.

PRGF: Therapeutic applications in different medica

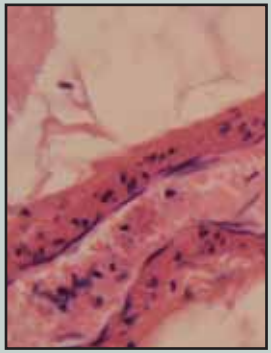


Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of sites for implants. Int J Oral Maxillofac Impl 1999;14:529-535

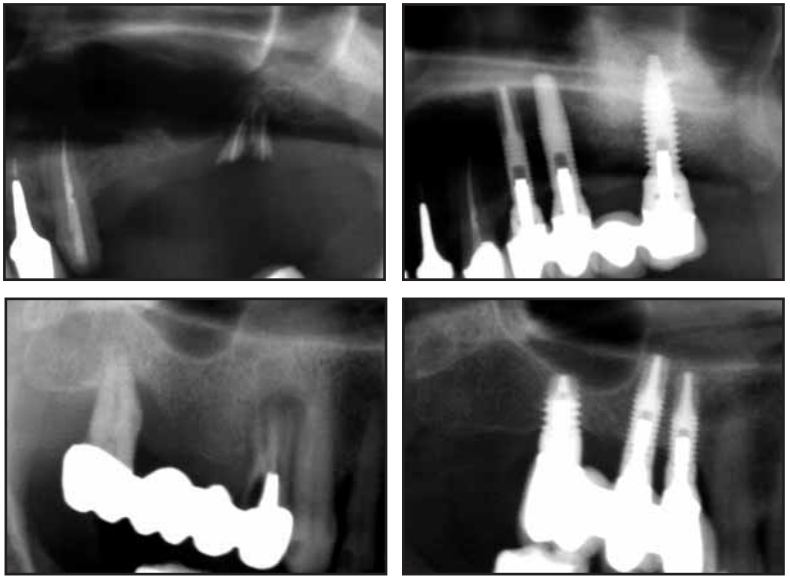
fields

This is one the most cited research papers about platelet rich preparations. The current article presents some preliminary clinical evidence of the beneficial effect of the use of plasma rich in growth factors of autologous origin. The protocol for obtaining the PRGF is described in detailed and some of the most important growth factors secreted by the platelets after PRGF activation are shown. Additionally, the microscopic and macroscopic results obtained with bone regeneration using this technology are illustrated. The scientific development and application of PRGF can introduce several important advantages in different fields and especially in dentistry and oral and maxillofacial surgery. This is mainly due to the acceleration of bone regeneration and the more rapid and predictable soft tissue healing obtained after PRGF application.

PRGF: Therapeutic applications in different medica



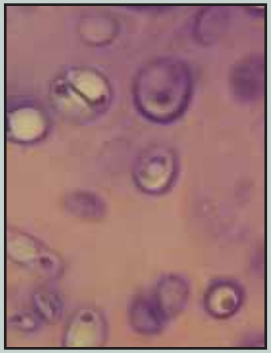
Anitua E. The use of plasma rich growth factors in oral surgery. Pract Proced Aesthet Dent 2001;13:487-493



fields

This is one of our first contributions in which the potential therapeutics effects of PRGF on tissue regeneration were analyzed. In many situations and clinical disorders, the unaided regeneration process is insufficient to allow complete repair of both bone and soft tissues. In this contribution we presented and discussed 2 clinical cases in which Preparation rich in growth factors is applied at the surgical site in order to stimulate regeneration of osseous and epithelial tissues. In both cases, we demonstrated the potential benefits of PRGF as an adjuvant in regenerative medicine. This preliminary research may open, in the following years, new avenues not only in dentistry and oral implantology but also in other medical areas including oral and maxillofacial surgery, treatment of chronic ulcers, eye disorders and especially musculoskeletal disorders.

PRGF: Therapeutic applications in different medica

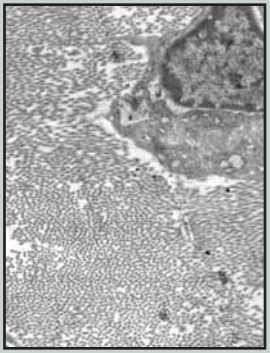


Sánchez M, Azofra J, Anitua E, Andía I, Padilla S, Santisteban J, Mujika I. Plasma Rich in Growth Factors to treat an articular cartilage avulsion: a case report. MSSE 2003;35(10):1648-1652.

fields

The potential value of PRGF is attributed to the slow delivery of growth factors from the platelets embedded within the fibrin matrix formed after the addition of calcium chloride. This case report described for the first time in the world the application of autologous plasma in arthroscopic surgery. An adolescent soccer player suffered a nontraumatic avulsion of articular cartilage in the knee. After arthroscopic reattachment of the large (>2 cm) chondral body in its crater in the medial femoral condyle, PRGF was injected into the area between the crater and the fixed fragment. Despite the extremely poor prognosis of the case, complete articular cartilage healing was considerably accelerated, and the functional outcome was excellent, allowing a rapid resumption of symptom-free athletic activity. These promising results opened new perspectives for cartilage regeneration.

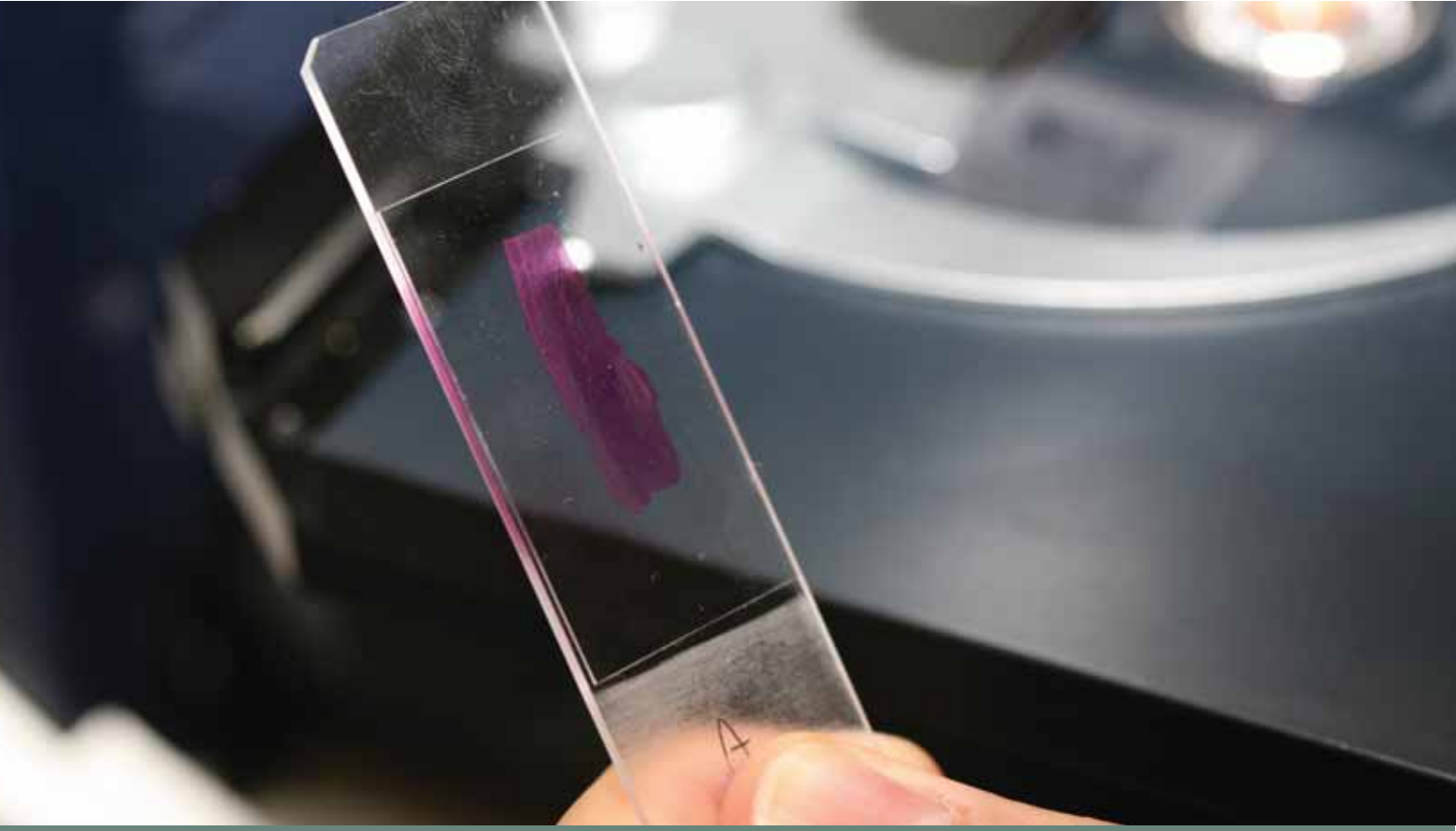
PRGF: Therapeutic applications in different medica



Sánchez M, Azofra J, Aizpurúa B, Elorriaga R, Anitua E, Andía I. Use of autologous plasma rich in growth factors in arthroscopic surgery. Cuadernos de Artroscopia 2003;10:12-19.

fields

This article describes a novel method for reconstructing the anterior cruciate ligament (ACL) using autologous plasma rich in growth factors (PRGF) during arthroscopic surgery. The two-step procedure includes priming and soaking the tendon graft with PRGF prior to insertion and then introducing PRGF into the target bone tunnels aiming to enhance the growth of bone and the overall healing process. Clinical outcome was prospectively evaluated in a total of 100 patients. Postoperative complications and inflammation were reduced with the use of PRGF. Moreover biologic remodelling and incorporation of the tendon graft within the tunnel were enhanced in the group treated with PRGF. This study suggests that benefits derived from this new procedure will contribute to a good prognosis and improved clinical outcome.



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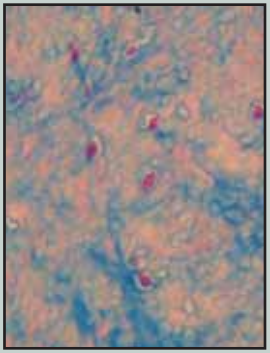
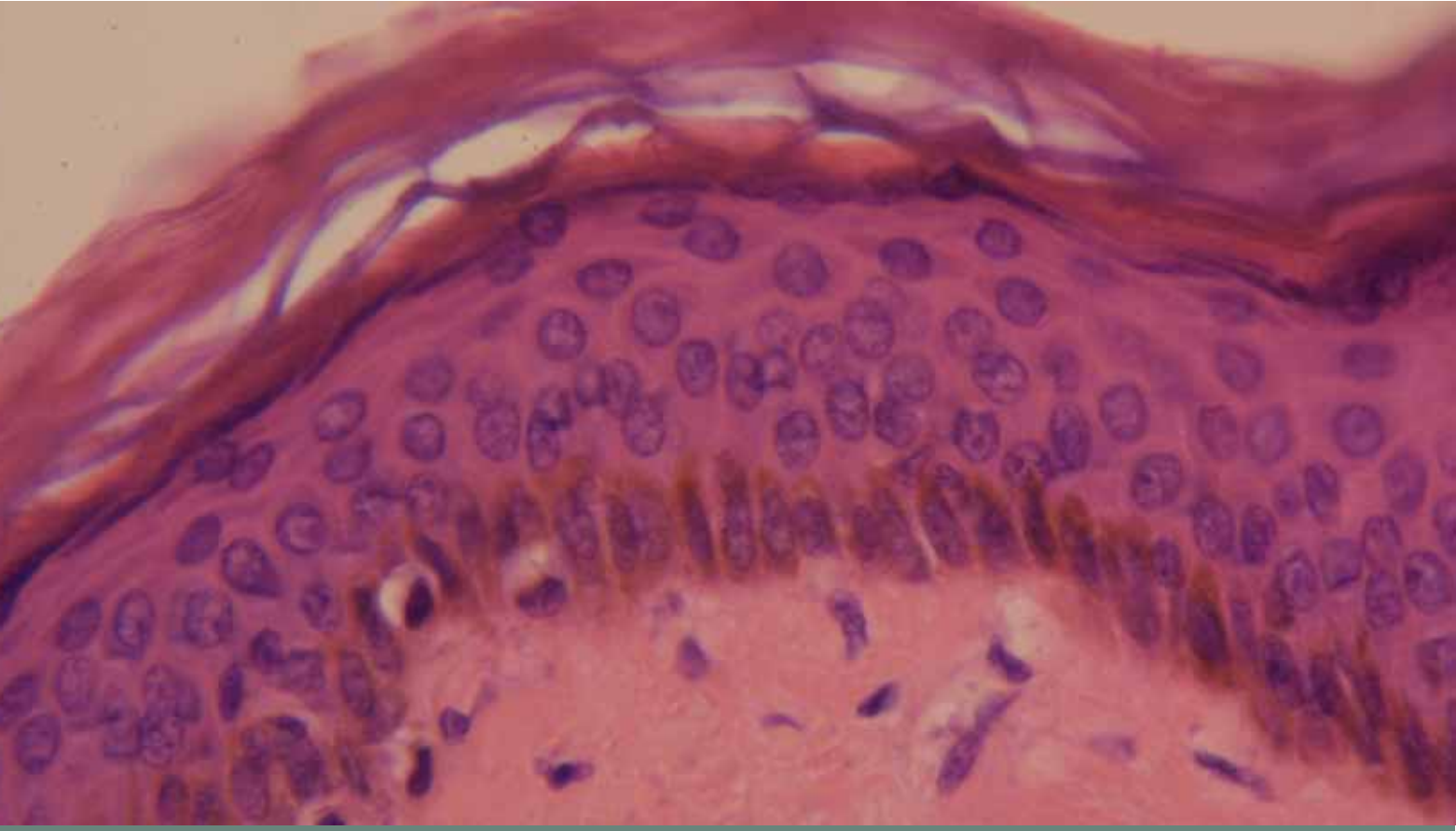


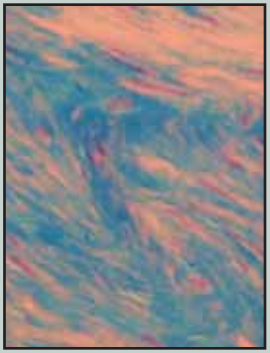
Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using PRGF. Am J Sports Med 2007;35(2):245-251.

fields

A case-control study was performed to examine the beneficial effects of PRGF during surgical reconstruction of Achilles tendon ruptures. Twelve athletes underwent open suture repair after complete tear. Open suture repair in conjunction with a Preparation Rich in Growth Factors (PRGF) was performed in six athletes and retrospectively compared with a matched group that followed conventional surgical procedure. The outcomes were evaluated on the basis of range of motion, functional recovery and complications and tendon morphology evaluated by ultrasound. Moreover a laboratory descriptive study aiming to characterize PRGF by number of platelets and concentration of insulin (IGF-I), transformed (TGF-ß1), platelet-derived (PDGF-AB), vascular endothelial (VEGF), hepatocyte (HGF) and epidermal (EGF) growth factors was performed in patients affected by musculoskeletal traumatic injuries. Athletes receiving PRGF recovered the range of motion earlier, showed no wound complication and acceleration in the time necessary to take up gentle running and to resume training activities. Moreover the PRGF treated tendons' cross-sectional area increased less pointing out to a more physiological repair. Application of PRGF during surgical reconstruction of tendons presents new possibilities for enhanced healing and functional recovery.



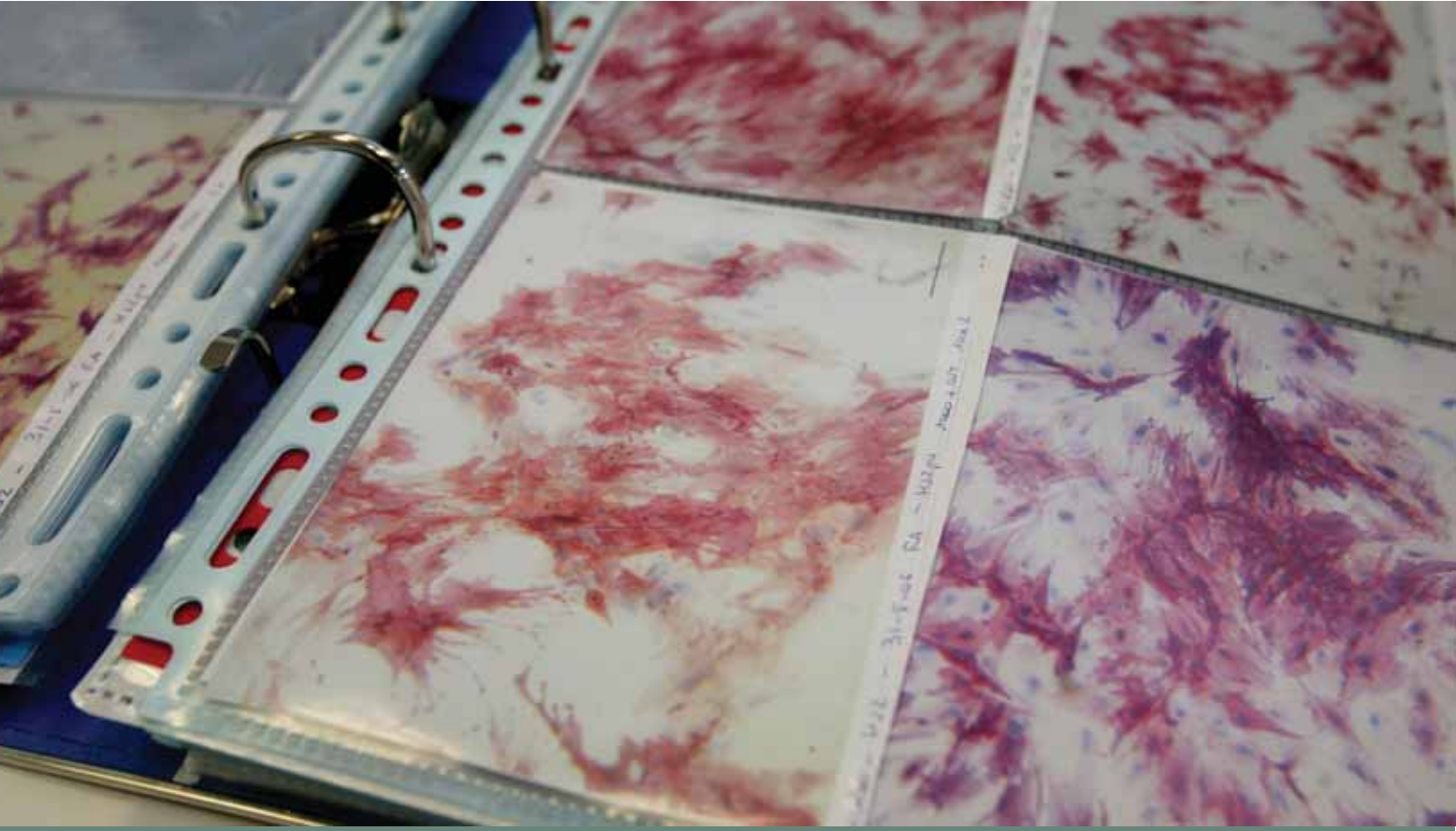
PRGF: Therapeutic applications in different medica



Anitua E, Aguirre JJ, Algorta J, Ayerdi E, Cabezas AI, Orive G, Andía I. Effectiveness of autologous preparation-rich in growth factors for the treatment of chronic cutaneous ulcers. Submitted 2007

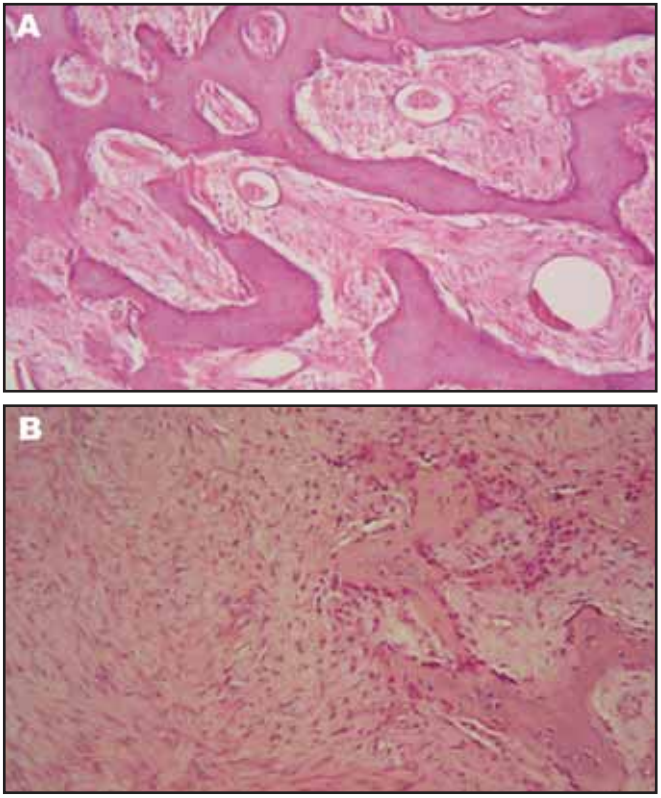
fields

The objective of this study was to assess the effectiveness and safety of a preparation rich in growth factors (PRGF) for the treatment of chronic cutaneous ulcers. Aiming to characterize PRGF, quantitative aspects including platelet count and PDGF-AB, TGF-b1, IGF-I, HGF, VEGF-A, and EGF concentrations were examined in 25 healthy donors. A randomized open-label controlled pilot trial was undertaking with fifteen patients. assigned randomly to either topical application of PRGF or standard care (wound cleansing, debridement, and moist saline gauze dressing). A total of 14 ulcers were assessed (64% venous leg ulcers, 29% pressure ulcers, and 7% other). Both groups were comparable at entry. At 8 weeks, the mean percentage of surface healed was significantly greater in size in the PRGF group than in the standard care group ($P < 0.05$). Within the limitations of a pilot study, topical application of PRGF is more effective than standard therapy in helping a chronic ulcer to heal.



PRGF: Therapeutic applications in different medica

Anitua E, Orive G, Plá R, Román P, Serrano V, Andía I. The effects of PRGF on bone regeneration and on titanium osseointegration in goats: a histologic and histomorphometric study. (Submitted 2007)



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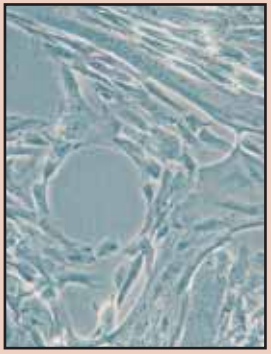
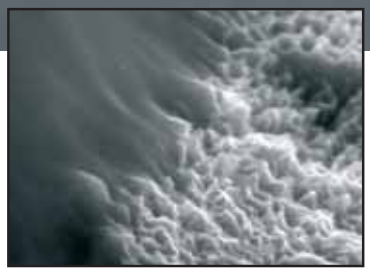
The effect of local application of autologous preparation rich in growth factors (PRGF) on bone regeneration in artificial defects and the potential effect of humidifying titanium dental implants with liquid PRGF on their osseointegration were investigated. PRGF was obtained from venous blood of 3 goats and applied either as a fibrin scaffold in the regeneration of artificial defects and as PRGF liquid via humidifying the implants before their insertion. Initially, 12 defects were filled with PRGF and another 12 were used as controls. The histological analysis at 8 weeks revealed mature bone trabeculae with osteocytes inside when PRGF was used whereas the control samples showed mainly connective tissue with incipient signs of bone formation. For the second set of experiments, 26 implants (13 humidified with PRGF) were placed in the tibiae and radii of goats. Histological and histomorphometrical results demonstrated that application of liquid PRGF increased the percentage of bone in contact with the implant in 84.7%. In fact, the whole surface of the PRGF-treated implants was covered by newly formed bone whereas only the upper half was surrounded in control implants. Assuming these results, it was concluded that PRGF can accelerate bone regeneration in artificial defects and improve the integration of titanium implants in trabecular bone.

Dental implants BTI®



Anitua E. Enhancement of osseointegration by generating a dynamic implant surface. J Oral Implant 2006;32:72-76.



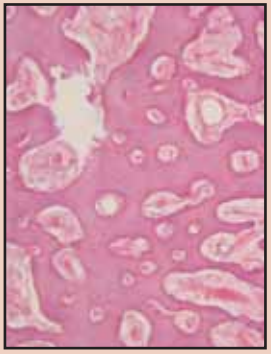
Preparation rich in growth factors (PRGF) can be used to promote healing and tissue regeneration. In the present research article we evaluated the effect of covering the titanium implant surface with this autologous preparation with the aim of enhancing implant osseointegration. The interaction of PRGF with the surface of titanium implants was examined by environmental scanning electron microscopy (ESEM). A total of 23 implants were placed in the tibiae and radii of 3 goats, 13 of them were inserted after covering the surface and filling the alveolus with PRGF whereas the other 10 were installed following a conventional protocol and served as controls. Histomorphometric analysis of the bone-implant interface was done 8 weeks later. One of the most important discoveries of the present work was to demonstrate that implant surface adsorbed the protein-rich material. Furthermore, the in vivo experiments showed clearly that osseointegration was improved when PRGF was employed to humidify the surface of the implants. Therefore, the bioactivation of the dental implant surfaces by generating a nano-biological coating on the titanium surface may have important clinical implications for dentistry in the aim of improving the prognosis and predictability of oral implantology.

Dental implants BTI®

Anitua E, Orive G, Aguirre JJ, Ardanza B, Andía I. 5-year follow up of BTI dental implants: risk factors for implant failure. Submitted 2007

The aims of this study were to evaluate the long-term results of BTI® implants using implant loss as outcome variable and making an implant-based and patient-based analysis of failures, and to identify in a statistical efficient manner the risk factors associated with implant failure. To address these issues, a retrospective cohort study design was used. 1060 patients received 5787 BTI® implants during the years of 2001-2005 in Vitoria, Spain. The potential influence of demographic items, clinical items, surgery-depending items and prosthetic variables on implant survival was studied. Implant survival was analysed using a life-table analysis. Cox proportional hazards regression was employed to identify risk factors related to implant failure. According to the results obtained, the overall survival rates of BTI® implants were 99.2% and 96.4% for the implant and patient-based analysis respectively. Totally, 28 out from 5787 implants (0.48%) were lost during the observation period. Most of the patients (70.8%) with implant failure presented a moderated or advanced periodontitis. Smoking habits, implant position, implant staging (two-stage implants) and the implementation of special techniques were statistically correlated with lower implant survival rates. Two risk factors associated with implant failure were detected in this study: implant staging (two-stage implants) (OD= 2.25, $p<0.038$, 95% CI= 1.05 to 4.84) and the use of special techniques (OD= 0.4, $p<0.02$, 95% CI= 0.19 to 0.87). These data clearly indicate that treatment with BTI® implants is safe and predictable.

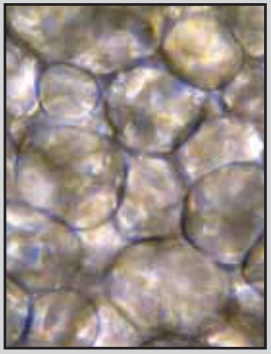
Dental implants BTI®



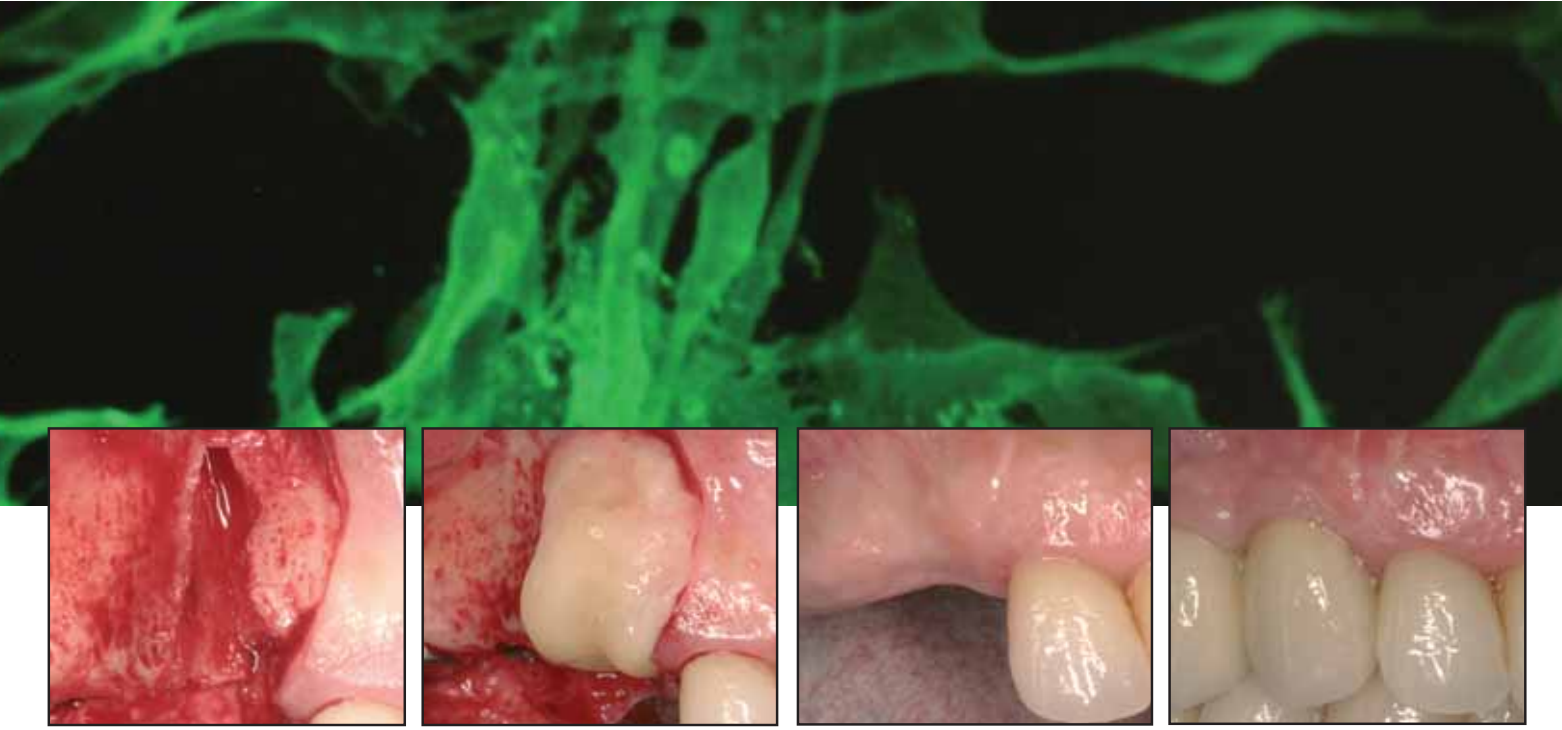
Anitua E, Orive G, Aguirre JJ, Andía I. Clinical evaluation of short BTI dental implants placed in posterior areas: a 5 year retrospective study. Submitted 2007

The aims of this study were to evaluate the long-term success and survival rates of short BTI implants in posterior areas and to analyze the influence of different items on implant survival. For the present article, we made a retrospective cohort study design. 357 patients received 643 short BTI implants during the years of 2001-2005 in Vitoria, Spain. All implant installations were performed by two experimented surgeons and rehabilitations were done by 3 prostodontists. Each implant failure was carefully analyzed and the potential influence of demographic items, clinical items, surgery-depending items and prosthetic variables on implant survival was studied. Implant survival was analysed using a life-table analysis. Our data indicated that the overall survival rate of BTI implants was 99.2%. The mean follow-up period for all 357 patients was 27.02 14.1 months. Average marginal bone loss during the 5-year follow up ranged between 0.5 and 0.7 mm. Totally, 2 out from 643 implants were lost during the observation period due to cantilever overload and implant insertion in bone type IV. None of the variables studied resulted to be statistically associated with implant failure due to the reduced number of failures. The information provided in this study might help clinicians to improve their decision-making with the aim of enhancing implant success.

Innovation of protocols and surgical techniques

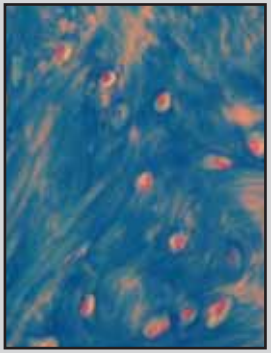


Anitua E, Orive G, Andía I. A novel clinical predictable protocol for the treatment of post-extraction defects. (Submitted 2007)



The purpose of this study was to evaluate the biosafety, efficacy and predictability of a new clinical protocol aimed to ensure complete healing and bone regeneration of the post-extraction defects and the insertion of dental implants with high primary stability. Fourteen patients who underwent tooth extraction in defects of different size and anatomical position received this protocol consisting on biological, radiological and mechanical procedures. Fresh extraction sockets were filled with preparation rich in growth factors (PRGF) and sealed with autologous fibrin. The growth factors released from the PRGF prepared from each patient was measured for optimal characterization. At 12-16 weeks post-extraction, mean bone densitometries in the inner and outer perimeter of the defects were measured using BTI scan® program resulted in 519±211 Hounsfields (HU) and 589±170 HU respectively. Different BTI® implants in length and diameter were humidified with PRGF and installed in the regenerated defects. The primary stability of the implants revealed a mean insertion torque of 51±8 Ncm, which confirmed their high primary stabilities. Results confirmed that this new clinical protocol is safe, effective and predictable for installing dental implants with high primary stability in post-extraction defects. The combination of biological and radiological procedures with stability measurements of the primary implant stability constitute a powerful protocol which will improve the clinical decision making of implant therapy.

Innovation of protocols and surgery techniques



Anitua E, Carda C, Andia I. A novel drilling procedure and subsequent bone autograft preparation: a technical note. Int J Oral Maxillofac Impl 2007



This study was undertaken to evaluate a new drilling system providing autologous bone chips that, when associated with a plasma rich in growth factors (PRGF), serves as a grafting material for bone regeneration that is beneficial to subsequent implant procedures. The new drilling system, used in conjunction with specifically designed drills is compared to the conventional procedure. Bone particles collected using both systems in the same ten patients are analysed by means of optic and electronic microscopy. The histology and ultrastructural analysis showed conserved structure and the presence of living cells in the bone chips of all samples obtained from drilling at low speed, whereas the material obtained by conventional drilling does not maintain these qualities. Collected bone mixed with PRGF is later used to fill bone imperfections. The new drilling procedure has been developed based on biological criteria. The method reduces damage to the host tissue and obtains a mass of living bone for subsequent grafting in association with autologous growth factors. This study suggests that benefits derived from this new procedure will contribute to a good prognosis and improved clinical outcome.

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