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Classification and algorithm proposal for the orthobiological management of bone loss. New therapeutic approach

Propuesta de clasificación y algoritmo del manejo ortobiológico de las pérdidas óseas. Nuevo enfoque terapéutico

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Abstract

Through the signaling of growth factors, osteoprogenitor cells and the extracellular matrix as a natural scaffold, bone consolidation is achieved. Bone regeneration can be affected by mechanical or biological factors. The diamond concept is to have osteoinductive mediators, osteogenic cells and osteoconductive matrix (scaffold), as the framework for a successful bone repair response, mainly based on mechanical stability and biological environment, through adequate vascularity and optimal physiological state of the host. There are systematic reviews that support the use of polytherapy with orthobiologics under the diamond concept in acute fractures, delayed union and non-unions. There are several options for the management of bone loss: the application of autograft with collagen sponge, placement of autologous tricortical iliac crest block, the induced membrane technique, intercalary segment allograft, vascularized fibular graft and bone transport. We propose a classification/algorithm as a treatment guideline according to bone loss, aseptic or septic, using the best orthobiological elements and techniques available in the literature, optimizing the mechanical and biological environment to achieve consolidation and the bone salvage.

Keywords: bone loss, algorithm, classification, platelet-rich plasma, bone marrow, graft.

Resumen

Por medio de la señalización de factores de crecimiento, las células osteoprogenitoras y la matriz extracelular como andamio natural, se logra la consolidación ósea. La regeneración ósea puede ser afectada por factores mecánicos o biológicos. El concepto diamante es contar con mediadores osteoinductivos, células osteogénicas y matriz osteoconductiva (andamio), siendo este el marco de referencia

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para una respuesta exitosa en la reparación ósea, basado principalmente en la estabilidad mecánica y en el ambiente biológico, mediante una adecuada vascularidad y un óptimo estado fisiológico del huésped. Hay revisiones sistemáticas que apoyan el uso de politerapia con ortobiológicos bajo el concepto diamante en fracturas agudas, retardo en la consolidación y pseudoartrosis. Existen diversas opciones para el manejo de las pérdidas óseas: aplicación de autoinjerto con esponja de colágeno, colocación de bloque de cresta iliaca tricortical autólogo, la técnica de membrana inducida, aloinjerto en segmento intercalar, injerto de peroné vascularizado y transporte óseo. Proponemos una clasificación/algoritmo como guía de tratamiento de acuerdo con el tamaño de la pérdida ósea, aséptica o séptica, utilizando los mejores elementos ortobiológicos y técnicas que hay en la evidencia literaria, optimizando el ambiente mecánico y biológico para lograr la consolidación y el rescate óseo.

Palabras clave: *pérdida ósea, algoritmo, clasificación, plasma rico en plaquetas, médula ósea, injerto.*

Introduction

Bone is one of the few organs that maintains the potential for regeneration in adult life. There are three main components for achieving bone consolidation: growth factor signaling, osteoprogenitor cells, and the extracellular matrix/natural scaffold.[1] These are the three biological prerequisites for fracture healing, thus the so-called «diamond concept» is formed by a complex triangular figure of interactions between osteogenic cells, osteoinductive stimuli, and osteoconductive matrix scaffolds, and also a fourth element, which is mechanical stability, crucial for bone consolidation.[2]

The polytherapy approach called the «Diamond Concept», designed by Giannoudis and colleagues, provides guidance for the minimum requirements necessary to optimize bone healing, including osteoconductive scaffolds, osteogenic and angiogenic cells, osteoinductive mediators, and adequate mechanical environment.[3]

The area of where the bone defect is, is the heart of the diamond concept. This area is where the bone repair process will take place and will be called «the biological chamber», whose properties include vascularity for transporting and supplying oxygen, nutrients, signaling molecules, and the migration of osteoprogenitor cells.[2] The diamond concept has proven itself to be an important framework for understanding the minimum requirements for bone healing, and it is also very useful when planning the surgical management of nonunion fractures in both upper and lower limbs.[4]

Modern treatment strategies use a combination of graft and bone substitutes to be placed at the site of the bone loss. There are several indications for the use of bone graft, such as in traumatic defects, as part of bone defect management like in the Masquelet technique, and to improve the biological activity of an atrophic nonunion. The success of healing with bone grafts lies in using the diamond approach as a conceptual framework, by providing osteogenic cells, osteoinductive mediators, an osteoconductive matrix, mechanical stability, and adequate vascularity.[5]

The term «composite graft» refers to the combination of different materials to increase the biological properties and volume of the bone graft.[6] Materials that can be used include autologous bone graft, allograft, BMP-2, PRP, bone marrow aspirate, xenograft granules, and isolated synthetic granules or those with collagen matrices.[7] This approach has been popularized within the conceptual framework of the diamond concept to optimize biological stimulation, known as polytherapy.[5] The efficacy of polytherapy via composite grafts has been reported by Giannoudis and colleagues, through the application of the diamond concept using the polytherapy approach, the authors achieved consolidation in 98% with a mean of six months.[8]

The objective of proposing a classification and algorithm for orthobiological management of bone losses is to have an organized treatment approach guide based on the size of the bone loss, whether it is infected or not. This involves understanding the properties of each orthobiological element and mandatorily applying the diamond concept. The priority is given to the technique or techniques that, according to current literature, have the lowest percentage of complications and the greatest possibility of achieving bone consolidation and rescue.

Diamond concept

The diamond concept refers to the availability of osteoinductive mediators, osteogenic cells, osteoconductive matrix (scaffold); an optimal mechanical environment; adequate vascularity and targeting in case of the existence of any host comorbidity.[1,2] A complex polytherapy approach called the «diamond concept», this provides a guideline for de minimal requirements needed for efficient bone healing. Each component within this approach plays a critical role in the overall ability of the biological substitute for bone healing and regeneration. The biomaterial scaffold acts as a 3D microenvironment for cells by providing structural support, porous to allow for cellular migration and vascular network infiltration.[3] The biological chamber, the heart of the diamond concept, is based on the need for containment. This chamber allows an influx of biological activities to promote healing in a timely manner. That is, the development of a bioreactor[1-4] *(Figure 1)*.

The success of fracture consolidation depends on the biological environment of the fracture site (availability of mediators, progenitor cells and matrix, immunoregulatory cells, among others) in addition to an optimal mechanical environment that provides adequate stability, facilitating the successful evolution of the physiological process of bone repair. The diamond concept is the reference framework for a successful response in bone repair, giving importance to both mechanical stability and the biological environment. Adequate vascularity and the physiological state of the host are essential for fracture repair.[4]

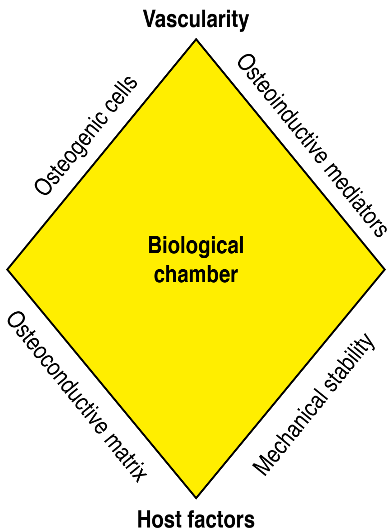

Figure 1: Diamond concept.

First of all, we must know and understand the mechanism of action and efficacy of scaffolds, growth factors and cell therapies in bone healing stimulation of diaphyseal fractures.

The autograft combines all properties required in a biological graft: osteogenic, osteoconductive and osteoinductive properties. The allograft the main disadvantage is the loss of osteogenic potential, having osteoconductive properties. The demineralized bone matrix preserves collagens, non-collagenous proteins and growth factors, having osteoinductive and predominantly osteoconductive properties. The Platelet-rich plasma has predominantly osteoinductive properties. The bone marrow aspirate concentrate has osteoinductive and predominantly osteogenic properties[5,9] *(Figure 2)*.

Synthetic growth factors, including bone morphogenetic protein, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), bone morphogenetic protein-2 (BMP-2) and bone morphogenetic protein-7 (BMP-7) regulate the activity of osteoprogenitor cells and their differentiation into osteoblasts, stimulate chondrocyte proliferation in endochondral bone formation. Fibroblast growth factors are secreted by monocytes, mesenchymal stem cells, osteoblasts, and chondrocytes; from the early stages of fracture

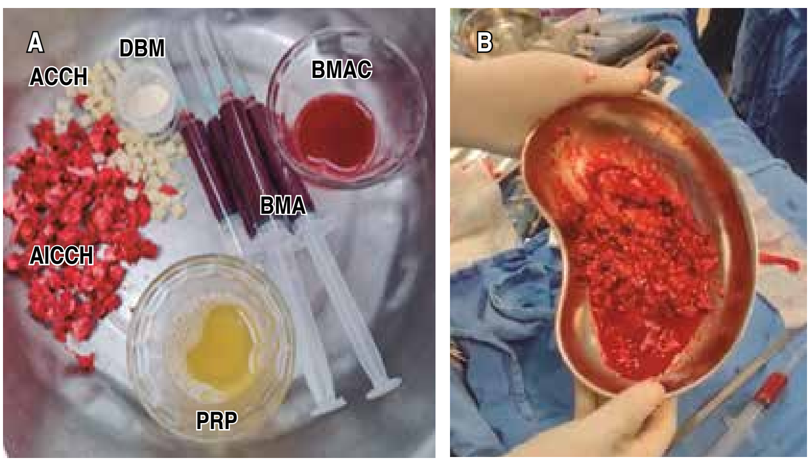

Figure 2:

A) Orthobiological elements: AICCH = autologous iliac crest cancellous chips, ACCH = allograft cancellous chips, DBM = demineralized bone matrix, BMA = bone marrow aspirate, BMAC = bone marrow aspirate concentrate, PRP = platelet-rich plasma. **B)** Diamond blend or composite graft.

healing through the healing process. They have been found to shorten healing time with high rates of consolidation.[9]

The gold standard for augmenting bone healing remains autologous bone graft, however, limitations in volume mean that combination with other techniques is often required to achieve successful union. The concept «composite graft» (polytherapy) refers to the process of combining different available materials in order to increase the biological properties and the volume of bone graft, being a sensible option for one to consider for the treatment of recalcitrant non union, critical size bone defects, and in patients with compromised biological host responses. Enhancing the biologic properties and potency of a graft material appears to generate powerful osteogenic and angiogenic conditions[5] *(Figure 2)*.

In the last decade, the «diamond concept», has given equal importance to the mechanical stability and the biologic environment, and offered a new paradigm for complex fractures and impairment union management. Additional local biological enhancement by addition of a scaffold, growth factors, and cell therapies whilst preserving the local vascular supply. The evidence available nowadays showed convincing results supporting the use of «polytherapy» with the diamond concept over «monotherapy».[9]

Bone consolidation and risk factors

In long bone fractures the displacement, comminution and disruption of the vascular supply that affects the healing process, in addition to severe bone defects, soft tissue damage, open fractures and the risk factors of each patient; lead to non-unions or delayed union, which ranges from 1.9 to 10% of diaphyseal fractures.[9]

Risks of non-union can be defined as patient dependent and independent, as well as local and systemic, some of which can be modified to enhance fracture healing.[4]

Risk factors for bone healing: age: in older adults the periosteum is fibrous and causes slower callus formation, osteoporosis: due to decreased estrogen receptor expression, there is low production of growth factors, as well as mesenchymal cell deficiency. Poorly controlled diabetes: poor vascularization that promotes soft tissue damage, delayed consolidation and non-union. Smoking: nicotine inhibits cell proliferation during the repair process, acts as a vasoconstrictor, therefore, perfusion damage, hypoxia and ischemia. Alcoholism: > 1,000 cm^3 per day of ethanol inhibits ossification in bone formation. Use of NSAIDs for a period > 4 weeks immediately after surgery, reduces osteoblastic activity and inhibits prostaglandin synthesis. Nutrition: amino-protein malnutrition negatively affects consolidation. Vitamin D: its supplementation has been shown to stimulate osteogenesis, increase the production of osteocalcin and stimulate bone resorption mediated by osteoclasts. There are other risk factors that alter bone healing such as reduced muscle mass, sarcopenia, calcium, postmenopausal women, genetic polymorphisms and fracture-related factors such as high-energy trauma, soft tissue injury, open fracture with high Gustilo-Anderson classification grade, large interfragmentary spaces, complex fractures and biomechanical comminutability, large fracture hematoma, infection and prolonged immobilization.[9]

Under certain conditions, there may be a need to try and enhance fracture repair, be that in the context of high-risk injuries, such as those with bone loss, or in the case of non-union where the fracture will fail to heal without further intervention.[5]

Clinical results of orthobiology in trauma

Acute fractures

Marongiu et al., in a systematized review of clinical evidence on the treatment of acute diaphyseal fractures with orthobiologics, included 1,350 patients, where the evidence shows convincing results supporting the use of combination therapy with orthobiological treatments in delayed union and non-unions; a few high-level studies and other reports demonstrated findings in favor of the application of the diamond concept in acute fractures. Vascularized and non-vascularized cortical autografts represent the ideal, due to their osteoinductive, osteoconductive and osteogenic properties and mechanical support function.[10]

Jamal et al, from a systematic review of 27 articles with 1,631 patients, in 13 studies evaluated the use of PRP in delayed union or non-union, seven studies in the management of acute fractures, four studies in osteotomies and tibial lengthening and three studies in lumbar spine pathology. Of these 9 level 1 randomized controlled studies, 16/27 studies evaluated PRP with other orthobiologics (autologous, allograft, BMAC, DMB, BMP-7, BMC, MSC), 11/27 studies only PRP, 18/27 studies reported a clinical benefit of PRP.[11]

Not only is BMAC indicated for nonunions, it should be strongly considered for primary arthrodesis and fractures, especially when the host is metabolically compromised.[12]

Delay in consolidation and non-unions

Orthobiologics are frequently used to increase fixation and improve the biology of bone healing, especially in atrophic non-union. Autologous bone graft is the most recommended treatment since it is osteoinductive, osteoconductive and osteogenic, although it is associated with comorbidities related to obtaining the graft. The use of BMAC plus DBM has shown excellent results in the treatment of atrophic non-union.[13] Hernigou et al, demonstrated an 88% cure rate in atrophic non-unions treated with percutaneous BMAC.[14] Desai et al, used DBM plus BMAC with a union rate of 86% at 4.5 months in atrophic tibial non-unions.[15] PRP has only shown good potential in the treatment of non-unions, reporting union rates of 87 and 9% in 2 studies.[13] Benshabat et al, in a retrospective study in a case series of 21 patients of non-union in clavicle fracture were treated with open reduction and internal fixation plus BMAC from 2013 to 2020 with a 36-month follow-up, 20 (95.2%) patients demonstrated union in 4.5 months, with good functional qualifications, without complications.[16]

Imam et al, in a Systematic Review of clinical applications and complications of BMAC in bone defects and non-unions; 40 studies, 15 of non-union, 18 of bone defects (including spine) and 7 studies of complications. They concluded that MSCs in BMAC have a self-renewal potential capable of differentiating into different musculoskeletal tissues. BMAC has been used to improve bone healing.[17]

Osteogenesis means the formation of bone by viable cells from the bone marrow or autograft. Osteoinduction describes bone formation by mitogenesis of undifferentiated perivascular mesenchymal stromal cells, leading to the formation of osteoprogenitor cells and osteoblasts. This is seen followed by transplantation of bone marrow autograft, demineralized bone matrix, bone morphogenetic protein BMPs, platelet-rich plasma, and autologous growth factors. Osteoinduction is a process where bone formation is enhanced by an appropriate structural environment, where osteoconductive material serves as a passive scaffold. This is pursued with autograft or allograft transplantation and demineralized bone matrix.[18]

Absorbable collagen sponge

Wang et al. describe a hemostatic sponge gelatin that can act as a scaffold for engineered bone tissue. Its characteristics of biodegradability, biocompatibility, and its ability to promote cell proliferation and migration, as well as osteogenic differentiation to preosteoblasts have been demonstrated.[19]

Collagen, especially type I, is an important organic component of natural bone. Its adequate biocompatibility, degradability, hydrophobicity, porosity, osteoconductivity and cell adhesion promoter, is widely used in bone and cartilage tissue engineering. Collagen, a natural polymer, is frequently modified by other materials into hydrogels constructs, scaffolds, sponges, microfiber/nanofibers, and microspheres/nanoparticles to improve biological and mechanical properties in the field of bone regeneration. Collagen-based compounds demonstrate a positive effect on cells (BMSCs, ADSCs, MC3T3-E1, HUVECs, etc.), drugs (alendronate, strontium ranelate, genetics, proteins and peptides); or growth factors (BMP-2, BMP-4, TGF-β1, VEGF, etc.) to lead to bone/cartilage regeneration or vascularization.[20] Collagen is capable of increasing bone mineral density, osteoblast maturation and proliferation. Elango et al, found that collagen treated with bone marrow stem cells and mature osteoblastic cells increased proliferation compared to controls. AmRMA osteogenic markers and protein expression increased significantly compared to control.[21] This suggests that collagen is able to promote stem cell differentiation and osteoblastic activity. Collagen scaffolds have been shown to be beneficial with respect to bone regeneration.[22] Absorbable collagen sponges act as a scaffold promoting early vascularization and osteoinduction they provide osteogenic cells, are biocompatible, and have the ability to adapt to bone.[23] Cho JW et al, found in 21 patients that using the induced membrane technique, bone graft with a central absorbable gelatin sponge, reduced the requirement for bone graft; and in 18 patients (86%) consolidated radiographically at 9.1 months on average. A circumferential bone graft around a central gelatin sponge in association with the induced membrane technique can be successfully applied in critical bone defects involving the metaphyseal and diaphyseal area of long bones for the treatment of osteomyelitis and open fractures. The advantages of this method are the limited availability of cancellous bone autografts and in defects that require large amounts of graft. Gelfoam is a gelatin sponge that is based on a type A purified pig gelatin, which is widely used for bleeding control and has proven biocompatible and biodegradable properties. It is completely absorbed in 4 to 6 weeks by the action of collagenases and subsequently phagocytizes its fragments. It is flexible and can be shaped in various ways with suitable mechanical properties. It has the capacity as a scaffold for osteoblasts, which can proliferate, differentiate and integrate inside the sponge within its porous structure.[24] In an *in vivo* study Finn et al, applied Gelfoam to assess its potential to regenerate bone in the iliac crest defect in dogs and two months later, bone formed in the defect to which Gelfoam was applied. Gelatin sponge residues were incorporated into the new bone, with no foreign body reaction present.[25] In a clinical study of seven patients, sponge gelatin was inserted into the maxillary sinus, successfully inducing bone formation.[24] Giles et al, in a case series study of distal femoral pseudarthrosis, reported that iliac crest autograft plus bone marrow aspirate covered with collagen gelatin sponge (Gelfoam) was used, achieving total consolidation within the first six months of postoperative treatment, highlighting its use as a scaffold in orthopedics, since in addition to functioning as a transporting surface for cells and growth factors from bone marrow aspirate, it works as a means of containment and union of the bone graft between both ends of the fracture. Thus, this important tool is a candidate to function as a biomaterial that facilitates cell differentiation and migration, demonstrating that patients had a faster and more effective consolidation, and this could be a treatment guideline for pseudarthrosis and bone loss and that it is a low cost and reproducible technique[26] *(Figure 3)*.

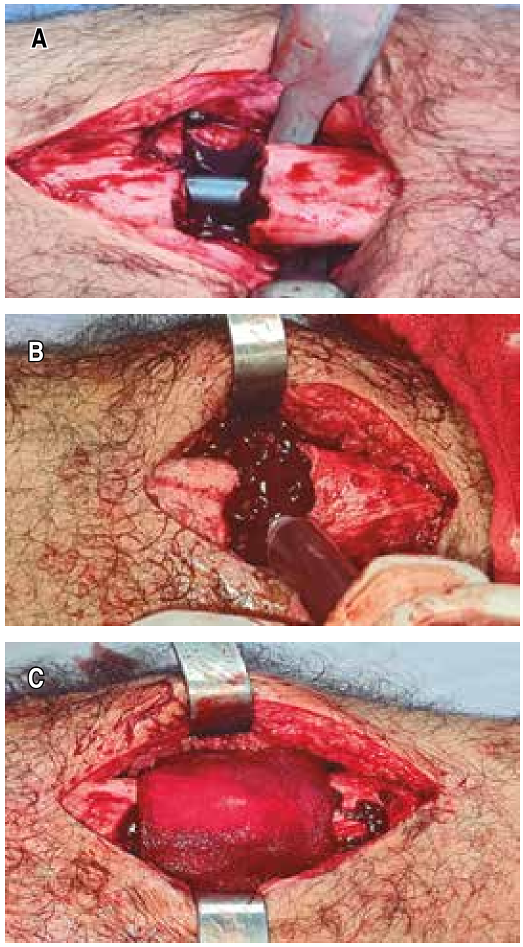

Figure 3: Type IA: **A)** Bone loss 3 cm with a intramedullary nail of tibia. **B)** Placing the bone marrow clot over the composite graft or diamond blend. **C)** Applying collagen gelatin sponge (Gelfoam) around and containing the composite graft.

Bone marrow aspirate

The iliac crest is considered the most suitable site for bone marrow aspirate.[27] Pierini et al, compared the concentration of MSCs between anterior and posterior iliac crest bone marrow aspirate in 22 patients, they found that the mean number of MSCs was 60% higher in the posterior crest than in the anterior crest, significantly. They concluded that taking the bone marrow from the posterior iliac crest is better.[28] This will depend on the position of the patient in surgery, the impossibility of placing the patient in the prone position, the familiarity of the surgeon with the anatomy of the iliac crest.[27] Hyer et al, demonstrated in a study that there are up to 898.4 MSC/mL in the iliac crest. This study confirmed that the iliac crest aspirate is the most appropriate.[29] Regarding the anatomy of the iliac crest, Hernigou et al, divided the length of the iliac crest into 6 different sections, each approximately 4 cm long. They found that sections 1, 4, and 5 are the thinnest sections, resulting in a high risk of cortical penetration, and that sections 2, 3, and 6 are the most suitable for the trocar, since they are thicker and safer.[30]

Neurovascular structures at risk: the external iliac artery in sections 1 and 2. Any trocar inserted in sections 5 and 6 in depth that is greater than 60mm and only 5 degrees of deviation at risk of cortical penetration, is possible injury in sciatic nerve and superior gluteal vessels.[27]

The size of the syringe: ideally, they should be 10 ml syringes, as Hernigou et al, found that the concentration of MSCs was 300% higher in aspirates with 10 ml syringes, since hypothetically the diameter of the syringe of 10 ml is less, which creates a high negative pressure, resulting in a higher MSC harvest. They recommend using low-volume syringes and aspiration at different sites.[27,31]

Aspirated volume: it is recommended to aspirate in volumes of 2 ml from one site. Muschler et al, found that the MSC concentration decreases by 28% in volumes of 1 to 2 ml and 38% between 2 to 4 ml.[32] Hernigou et al. found that, using 10 ml syringes, the MSC concentration decreased by 82% from 1 to 10 ml or from 2,062 to 376 MSCs/ml. Their conclusion was that aspiration of 10 to 20% of the syringe volume was ideal.[33]

Aspirate concentration: studies have shown that BMAC has a higher concentration of MSCs than non-concentrated aspirate.[27] The concentration of MSCs in bone marrow is 2,500 progenitor cells/cm^3 can be concentrated. Some have described primary fracture fixation with BMAC-enriched allografts for complex fractures and bone defects as an alternative to autografts. The role of BMAC in delayed consolidation or non-unions of long bones can be applied alone or in combination with scaffolds (autografts, allografts, DMB), PRP and BMPs.[9] Hernigou et al, centrifuged the bone marrow aspirate to separate the heavier polymorphonuclear layer. A 300 ml volume was reduced to 60 ml after the concentration process and the aspirate concentration increased from 612 to 2,579 MSCs/ml after concentration.[14] Although the concentrating process can optimize the success of the bone marrow aspirate in the treatment of non-unions, special equipment and increased surgical time are required, which can hinder this step. Successful results have been reported when unconcentrated bone marrow aspirate is performed, aspirated from multiple sites with aliquot volumes with small syringes, as well as taken from the posterior iliac crest.[27] (Bain and members of the British Society of Hematology, 2003) collected data that found that, in 55,000 procedures, only 26 adverse effects were reported, an incidence of 0.05%. The most frequent was hemorrhage and one death.[34] Hernigou et al, reported a complication rate of 7.6%. Complications such as anemia not requiring transfusion, persistent and early pain at the aspiration site, neuralgia, hematoma and seroma formation, superficial infection, aspiration site ossification, and aspiration site fracture. Compared with taking the iliac crest graft, which is 80.2%. They concluded that bone marrow aspirate is 10 times less complicated than iliac crest graft harvesting.[33] Hernigou et al, mention that bone marrow aspirate injection does not increase the risk of developing cancer in patients.[35]

Technique: immediately after anesthesiology has performed either subdural, epidural block or general anesthesia, the patient is placed in lateral decubitus, asepsis and antisepsis of the posterior region of the iliac crest is performed, sterile fields are placed and under Fluoroscopic control, Hernigou's section 6 of the posterior superior iliac crest is identified. The trocar (eg, Jamshidi or LeeLok needles) is inserted through a small incision, inserted to 6 cm depth, a heparinized syringe is attached to the trocar (5,000 units of sodium heparin diluted in 5 ml of saline are passed through the syringe before use to prevent the aspirate from clotting). Aliquots of 2 to 4 ml, rotating the needle 45^o, once fully rotated the needle is withdrawn 1 to 2 cm and the process is repeated. The needle is repositioned 2 cm from insertion for another round of multiple aspirations. A total of 2 to 5 separate sites within section 1 of the iliac crest is typically performed. The aspirate is used in the raw or concentrated state using a commercial or institutional centrifuge.[27]

Bone marrow aspirate clot

The use of fibrin clot has shown promising results. *In vitro* MSCs grown on fibrin gels have better proliferative potential and are able to maintain their differential osteogenic lineage potential compared to MSCs grown on plastic dishes, demonstrating that fibrin matrix can maintain stem cell ability to differentiate (stemness). The advantage of the fibrin clot from bone marrow aspirate to that of peripheral blood is that it has a high concentration of growth factors (VEGF, SDF-1 and FGF) and a high potential for osteogenic differentiation and fibroblast proliferation, positioning the clot of bone marrow aspirate as a candidate in regenerative medicine. Physiological aspects of bone marrow clot resemble fracture hematoma, which plays a significant role in bone healing.[36] This bone marrow aspirate clot is placed just after grinding the auto and allograft to be prepared and is mixed with them.

Plasma rich growth factors

Platelet-rich plasma is a suspension of autologous platelet blood concentrate obtained by centrifugation techniques. Growth factors, which are proteins released from platelet granules, among which we have transformed growth factor beta1 (TGFβ1), epidermal growth factor (EGF), VEGF, PDGF, FGF and IGF, which have been focused on improving the healing process of damaged tissues. Although a number of preclinical studies have reported favorable results in the use of PRP in acute fracture healing, its use in long bone fractures is mainly limited to delayed union and non-union. It has mainly osteoinductive properties.[9]

Blood extraction is performed prior to the surgical event. The extraction technique will depend on the system to be used (open or closed). From 20 to 40 ml of peripheral venous blood are extracted, it is centrifuged at a certain speed depending on the kit used, for example, the BTI PRFG-Endoret® system, requires centrifuging at 1,800 RPM or 580 g for 8 minutes.[37] PRP is divided into fraction 1 (F1), which corresponds to Platelet-Poor Plasma, which is the most superficial, and fraction 2 (F2), which corresponds to Platelet-Rich Plasma, which is below the Platelet-Poor Plasma and above the leukocytes.[38,39] There are different formulations or combinations of plasma that have growth factors. Formulation type 1 is non-activated, type 2 is activated with 10% non-coagulated calcium chloride, type 3 is activated and coagulated fraction 2, type 4 is activated and coagulated fraction 1, and type 5 is supernatant of fraction 1 and fraction 2. The fraction used in the preparation of the diamond mixture is used both activated and coagulated fraction 1 and 2 together, in addition to the supernatant, that is, type 3, 4 and 5 formulations are combined and are added to all the components of the diamond mix.[38,40]

Take autologous iliac crest graft

The available right or left anterior superior iliac crest graft is taken, or both, with an incision of approximately 10 cm, dissected by planes until locating the anterior superior iliac crest and approximately 7 × 4 cm are taken depending the size of the crest of each patient. It is recommended to take it from 3 cm towards the distal of the anterior superior iliac spine to avoid an avulsion fracture of the same. The block is taken and the spongy bone is extracted from the graft obtained, crushed with a gouge to a size of approximately 1 to 2 mm.[41]

Induced membrane technique, masquelet

The masquelet induced membrane technique (MIMT) has shown great promise in revolutionizing the repair of critical-size bone defects and has several advantages over distraction osteogenesis. A spacer cement is used to elicit a foreign body immune reaction, that induce a membrane to contain the autograft, which is placed in the defect by removing the stabilizing spacer.[42] This technique consists of two surgical times. During the first surgery, the injured tissue is removed and the bone is stabilized. The resulting space is filled with polymethyl methacrylate (PMMA). Whether antibiotics are included depends on the surgeon's preference; removing the infection is necessary for success; so the PMMA is supplemented with antibiotics. It is recommended to treat the infection with debridement and internal and/or external fixation. The membrane is the key to success of the technique, without it, grafts larger than 4 to 6 cm will be reabsorbed. The general recommendation is to perform the second surgical stage within 4 to 8 weeks;[42,43] however, this time depends on several circumstances such as the resolution of the infection, resolution of the damaged soft tissue, and transfer to a place with more resources. In the second surgical time, it is observed that the semi-permeable membrane is formed, which protects the graft from resorption and is very similar to the periosteum; however; it is thicker since it goes from 100 to 1,000 um. This membrane is composed of two layers, an innermost cell layer that is in contact with the spacer and the outermost fibrous. There is a third layer that is not always observed, with disorganized fibers. The inner and outer layers have type 1, 2, 3, and 4 collagen, growth factors, and cytokines. The rich vascular endothelial cell network has been observed in the membrane even in the disorganized third layer, similar to the collagen content, the density of vessels decreases with increasing age of the membrane. Initially not in contact with the graft, the proximity of the vessels is sufficient to rapidly invade the membrane compartment once the graft is implanted.[42] This membrane must be carefully and uniformly opened to be able to place the diamond concept mixture and then close the membrane perfectly and without tension to prevent the graft from coming out or being reabsorbed. There is no limit to the size of the defect to perform the technique, this depends on the surgeon's experience and adherence to detail in the two phases of the technique[43] *(Figure 4)*.

The advantages against osteogenesis by distraction or vascularized fibula, are that the patient accepts the treatment more, the reconstruction can be done with a plastic surgeon in the first surgical time, it does not require a vascular surgeon as in the use of vascularized fibula, there is greater adherence to the treatment, which is an advantage in the elderly and BMP-7 can be added. Complications of up to 49.6% have been reported, superficial infection of 4.9% and deep infection of 4.4%, persistence of infection and non-union of 18%, eradication of osteomyelitis in 91.1%, union and resolution of the defect in 89.7% in a range from 6 to 211 weeks.[44]

There is a classification of failures in the induced membrane technique, which are preventable by inappropriate assessment and failure of surgical tactics, such as septic (inappropriate bone debridement, soft tissue coverage, antibiotic treatment); mechanical (insufficient stability, insufficient filling of the cavity of the induced membrane); biological (failure to integrate the graft related to the use of tobacco, bone substitute, growth factors) and non-preventable failures or alterations in the biological properties of the induced membrane, physiologically it is the alteration of the remodeling of the extracellular matrix (MMP-9 deficiency, or circumstantial such as immunosuppressive therapy, anti-inflammatory drugs and excessive maturation of the induced membrane).[45]

Application of intercalary bone segments

Bone loss is called «Critical Size», when losing 2 to 2.5 the diameter of the bone. There is a Karger classification regarding the length of bone loss and it is divided into type I: < 20 mm; type II: 20-50 mm; type III: 50-100 mm; type IV > 100 mm. We must establish if the limb is salvageable. The application of bone segments has the advantage that it can be performed in one surgical time over the Masquelet or induced membrane technique, since the latter requires two surgical times to be carried out, so that the induced membrane can be formed. However, this use of intercalated bone segments can be combined with the Induced Membrane technique, being able to place the segment in phase II of the Masquelet, after carefully opening the formed membrane, the polymethylmethacrylate is removed and the intercalated segment is placed in the biological chamber, finally the induced membrane is sutured. Dheenadhayalan et al, in a study of 20 patients managed with gamma-irradiated intercalary allografts and autologous cancellous bone grafts in reconstruction of massive bone defects at the distal

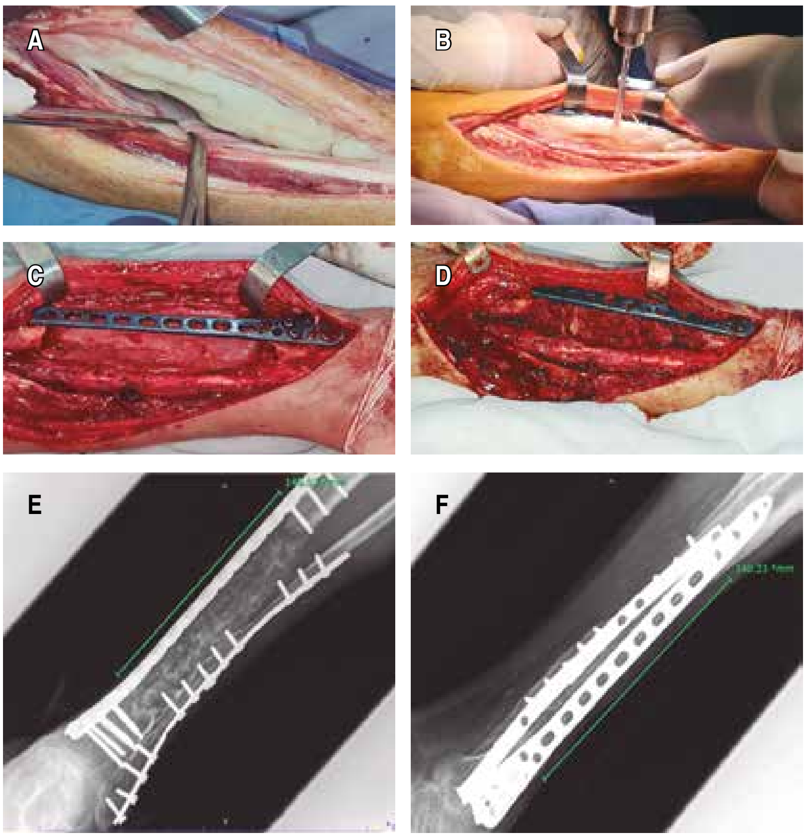

Figure 4:

Type IIIA: **A)** Masquelet technique phase I, opening de biological membrane. **B)** removing the polymethylmethacrylate with the drill. **C)** The biological chamber with 14 cm of length. **D)** The diamond blend or composite graft into the biological chamber. **E)** Anteroposterior X-ray of tibia and fibula with 13 months of follow up after the Masquelet technique. **F)** Lateral X-ray of tibia and fibula with 13 months of follow up after the Masquelet technique.

femur level consolidated at six months and at the proximal level at 11 months.[42,46,47] Jamshidi et al, in a meta-analysis and systematic review on how the type of osteosynthesis affects the complication rate in intercalary reconstruction with allograft, noted that with the use of centromedullary nailing, taking into account the location of the lesion in the femur, 65%, in tibia 32.4% and other locations mainly humerus in 2.6%, the percentage of non-union was 37%, fractures in 5%, infection 4%, local recurrences in 2% and with the use of plate, the percentage of non-union was 12%, the number of fractures was 11%, infection 11%, local recurrences 3%, concluding that centromedullary nailing is associated with a higher significant index of non-union and in any case, the index of fracture, infection and non-union is not significant between the plate and the nail fixation, therefore osteosynthesis with a plate should be considered the fixation method of choice for reconstruction of bone defects with intercalary allograft.[48] Errani et al, mention that in intercalary reconstruction after diaphyseal resection of bone tumors in a systematic review, that with allografts, 67 to 92% recover function, reporting non-union from 6 to 43%, fractures from 7 to 45% and infection from 0 to 28%, in terms of the use of allografts plus vascularized fibula, 86 to 94% recover function, with non-union from 0 to 33%, fractures from 0 to 44% and infection from 0 to 17%.[49] When reconstructing a diaphyseal bone loss with an intercalary allograft there must be stable fixation and a perfect union between the graft and the recipient bone to achieve adequate healing.[50]

Iliac crest in bone loss

In humeral shaft fractures, fixation can be augmented with biologics, including iliac crest graft, demineralized bone matrix, morphogenetic protein, or cancellous bone chip allograft. The use of bone autograft is preferred as it is the gold standard for biologic augmentation in non-union repair. Stevens et al. in the case of non-unions of the humerus, recommend the use of osteosynthesis with 4.5-mm LCP plates or 3.5 or 4.5-mm metaphyseal plates preferably, and can be selected according to the location of the fracture and the size of the humerus and autograft to promote the best healing change, giving absolute stability and creating an adequate biological environment. Using these strategies, humeral non-unions can have a cure rate of up to 98%.[51] In a systematic review, Peters et al,

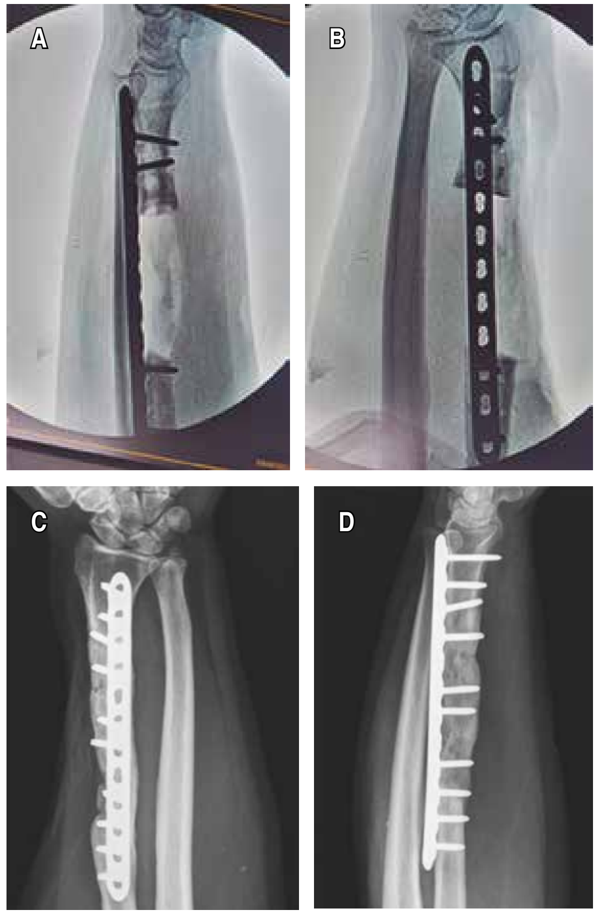

Figure 5: Type IIS: **A)** Lateral X-ray trans-surgical of radius and cubitus with bone loss 7 cm of length and < 3 cm of diameter. **B)** Anteroposterior X-ray trans-surgical of radius and cubitus with bone loss 7 cm of length and < 3 cm of diameter. *Pseudomona aeruginosa* infected. **C)** Anteroposterior X-ray of radius and cubitus with 24 months of follow up after Masquelet technique. **D)** Lateral X-ray of radius and cubitus with 24 months of follow up after Masquelet technique.

demonstrated a 98% union rate using plate and autograft, including 72 patients with a union time of 5.1 months.[52] Ambriz et al, reported a case of a 7 cm diaphyseal bone loss in the radius infected with *Pseudomonas aeruginosa*. Initially, they performed the Masquelet technique phase 1, filling the bone defect with cement containing gentamicin and vancomycin. After 16 weeks with the infection under control, they proceeded to phase 2 with the induced membrane technique, carrying out bone reconstruction by harvesting and applying two autologous iliac crest blocks, totaling 7 cm, along with a 12-hole 3.5 radius LCP plate and bone marrow aspirate, applying the diamond concept. They achieved complete consolidation at 10 months of follow-up, and the patient scored 100 points on the modified Mayo wrist functional scale[53] *(Figure 5)*.

The autologous iliac crest graft is the most appropriate since it has all the components of fracture healing, provides mechanical stability, is low cost, and has extensive support in the literature.[54]

Suction and irrigation reaming system

The iliac crest was, for a long period, the first choice for autograft harvesting, however, the reaming aspiration irrigation (RIA) system is becoming an increasingly popular device for harvesting and grafting the femoral canal. They have less donor site pain and large volumes can be harvested, although some problems have been encountered such as limited graft size selection, femoral neck fractures, and infections.[18] It is a novel system that takes the intramedullary reaming graft from the femur or tibial canal and suggests that it has osteoconductive and vascular properties equivalent to autologous iliac crest grafts, with potentially superior osteoinductive and osteogenic properties, being able to take large graft volumes with less morbidity and pain at the injection site.[54]

Vancomycin/polymethylmetacrylate

The addition of antibiotics in Polymethylmethacrylate spacers is controversial. Some reports do not recommend the use of medicated cement because it interferes with osteogenesis and the antibiotic may increase the risk of bacterial resistance in case of inadequate debridement. Some other studies have proposed the local use of antibiotics during the first phase is better to control the infection and repair the bone defect. Some studies mention that the membrane induced could be altered by different antibiotics. Due to the broad antimicrobial and thermostable spectrum, it is common to use Vancomycin in the Masquelet technique. Spacers with low concentrations of vancomycin 1 to 4 grams per cement dose (40 g) do not affect the angiogenic, osteogenic and proliferative capacity of the induced membrane. Some studies report that it can increase cell proliferation and osteoblastic viability. Concentrations above 6 grams per dose of cement can have negative effects on osteoblast viability, angiogenesis and induced membrane proliferation, having cytotoxic effects.[55]

Vascularized fibula graft

The use of vascularized grafts ensures that living cells are capable of inducing bone remodeling, allowing the implanted bone to integrate and consolidate. The vascularized fibula graft (VFG) is extremely effective in managing bone loss due to its high density of cortical bone and vascular supply. The VFG can include skin, fascia, and muscle if soft tissue coverage is required. However, the VFG carries the risk of flap failure, such as stress fractures, non-union, infection, thrombosis in the anastomosed vessel, ankle deformity, and hallux flexion contracture. Feltri et al, conducted a review and meta-analysis including 110 articles covering 2,226 patients. Functional scale from the Musculoskeletal Tumor Society was reported in 31 studies, with an average of 25.6 points, with 30 points being the best. Overall, good results were found, documenting a union rate of 80.1% and a complication rate of 39.4%. The most common complications were fractures (24%), non-unions (10.3%), delayed consolidation (16.4%), infections (11.8%), and vascular thrombosis (5.3%). The donor site accounted for 10.7% of all complications, including hallux flexion contracture (28.2%), paresthesia (15.4%), dropped foot (12.8%), chronic pain (10.9%), valgus ankle deformity (7.6%), cutaneous necrosis (6.4%), neuropathies (6.4%), tendon pathologies (2.6%), ankle instability (2.6%), partial graft loss (2.6%), hematoma (1.9%), incisional hernia (1.3%), wound dehiscence (1.3%). A 24.6% reintervention rate and a 2.8% amputation rate were recorded. In conclusion, good long-term results were documented in both upper and lower limbs; however, the technique is complex and demanding, requiring highly specialized surgery, leading to a high number of complications on average. This should be considered when choosing the most appropriate approach for managing long bone defects.[56] VFG surgery is demanding, and defects smaller than 4 cm can be adequately treated using standard fixation methods with autograft or allograft.[57] Structural grafts are associated with a high risk of complications such as fracture, infection, and non-union due to their avascular nature.[58] Therefore, VFG may be a valid option for these complex cases.[56] Capanna's technique, developed in 1980, combines the massive bone allograft technique with contralateral free intramedullary VFG to provide greater stability and allow for early loading.[59]

In this review, 74.1% of the studies used free VFG for treating tibial defects, while 25.9% used pedicled VFG. Primary consolidation rates were 87.6% in the pedicled group and 79.3% in the free VFG group, complication rates were 47.8% in the pedicled group and 43.1% in the free VFG group, and reintervention percentages were 20.5% and 20.8%, respectively. VFG has proven to be a viable option for salvaging limbs with bone defects, especially for defects larger than 4 cm, although it has a high complication rate. Due to this, significant efforts have been made in recent years to find alternatives in the field of grafts, particularly the use of scaffolds with or without augmentation strategies capable of receiving bone for regeneration while avoiding complications related to the donor site and the difficulty in performing anastomosis, such as the risk of avascular necrosis. This, or other techniques, may represent an alternative to VFG treatment in the management of bone defects.[56]

Bone transport

Bone transport, which induces osteogenesis through distraction, has been one of the most widely used techniques for bone regeneration for several years. Within Feltri's et al, meta-analysis on bone transport comprising 25 studies involving a total of 676 patients with an average age of 35.4 years, the primary union rate was 91%, with an average external fixation time of 8.9 months. However, there was a 62% complication rate, a 19% reintervention rate, and an 8% failure rate. The disadvantages of bone transport are its duration over several months, requiring strict patient adherence to complete, and a high risk of complications. From this meta-analysis, it's evident that there's a primary union rate of 91 but a 62% complication rate, the majority of which were due to infections, particularly around the pin tract, mostly resolving without surgical treatment. Other significant issues include restricted joint mobility, limb length discrepancy, and deformity.[60]

Tong et al, conducted a comparative study on the effectiveness of the Masquelet technique versus Ilizarov bone transport in treating post-traumatic osteomyelitis-related bone defects in lower limbs. In their retrospective study of 39 patients, they concluded that both techniques yield satisfactory results. The Masquelet technique shows better functional outcomes, especially in femoral cases, while Ilizarov bone transport is preferred for limb deformities. The Masquelet technique is a better option for periarticular bone defects.[61]

Ren et al, concluded in a meta-analysis covering 13 articles from 2017 to 2020, totaling 711 cases of Masquelet technique and Ilizarov bone transport for infected lower limb bone defects, that the Masquelet technique has significant advantages. These include lower hospitalization costs, shorter consolidation time, early full weight-bearing, lower complication rates, and better postoperative quality of life compared to Ilizarov bone transport.[62]

Despite the global acceptance of bone transport, some patients cannot tolerate the lengthy treatment and associated complications, such as pain during stimulation, pin site infections, nail breakage, readmissions, and reoperations. This leads to social implications for months or years, bone consolidation failure, non-union, alignment loss, increased clinic visits, and higher exposure to radiation. Patients need to be informed about clothing limitations, the inability to sleep with family, impact on their sexual life, difficulties in narrow spaces, the daily commitment of using the distraction device, frequent pin site care, regular antibiotic use, and stiffness. It's been reported that defects of up to 25 cm fully consolidate within 12 months using the Masquelet technique, whereas bone transport would require at least double that time at a rate of 1 cm per month. Giannudis, suggests that the Masquelet technique and bone transport are not in competition but rather complementary. Surgeons may have excellent skills in one technique, naturally favoring it for their patients.[63]

Thakeb et al, conducted a prospective, randomized, controlled study involving 30 patients with infected non-unions in lower limb fractures, dividing them into two groups: one treated with bone transport and the other with bone transport plus the Masquelet technique. They demonstrated that the latter led to significantly faster consolidation, lower postoperative complication rates including non-union and recurrent infection, and fewer additional procedures despite the two surgical phases compared to bone transport alone.[64]

Diamond mix preparation steps

Based mainly on the diamond concept of Giannoudis et al:[1-5,9]

1. Crush the cancellous bone of the iliac crest until obtaining a size of each of the fragments, ideally up to 2 mm^3 in size.[65]
2. Separate the cortical bone and if we are going to use it as a graft, keep it as large as possible,

as sometimes it helps us to place it as a cortical wall, both as a graft and as a containment of the diamond mixture that we are going to place in our bone loss.[41]

3. The volume of autologous cancellous bone obtained from the iliac crest is observed. Immediately we place allograft chips, ensuring that we have 70% autologous graft volume and 30% allograft, taking into account that these chips are also crushed so that they have a size not larger than 2 mm^3.[43,65]
4. The bone marrow aspirate previously obtained at the start of surgery is left in 5 or 6 10 ml syringes. each; No anticoagulant is given, they are left to rest so they coagulate. This clot from the bone marrow aspirate contains fibrin, growth factors, and extracellular matrix proteins, as well as mesenchymal cells.[27,36]
5. Platelet-rich plasma is prepared and fraction, 1 and 2 activated together are obtained and allowed to coagulate, that is, formulations 3 and 4 and finally the supernatant are added to all the components of the diamond mixture.[37,38,40]
6. 10 ml of bone marrow aspirate concentrate is processed and obtained, depending on the commercial centrifuge to be used.[27]
7. Having crushed the autograft and allograft chips of a size no larger than 2 mm^3, 10 to 20 cm^3 demineralized bone matrix, activated platelet-rich plasma, bone marrow concentrate and finally the bone marrow aspirate is applied in the form of coagulum, applying it in the form of «ketchup sauce» and mixing with all the orthobiological elements, achieving a greater volume of the diamond mixture to be applied.[1-5,9,27,36]
8. Diamond mix can be used in the following treatment options depending on the amount of bone loss and previous complications the patient has had:

   a. The composite diamond mixture is wrapped with a collagen membrane (gelfoam pfizer) to be used in bone losses of less than 3 cm in a surgical time, as a means of containing the mixture and cell scaffolding.[19,20,22-24,26]
   b. Iliac crest block plus diamond mix: the iliac crest block is placed, depending on the bone loss and the amount of crest that we obtain in a block, usually they are losses not greater than 7 cm and due to the size they have been used in humerus, radius and ulna; plus ground diamond mix at the ends of the iliac crest block junction with implantation site.[1,2,9,41,51,52,66-70]
   c. Masquelet or induced membrane technique: in infected and non-infected bone losses, in losses greater than 3 cm, polymethylmethacrylate is used with or without antibiotic (gentamicin) and additionally 1 to 4 grams of powdered vancomycin per dose of cement, this is placed in both the polymethylmethacrylate and the soft tissues after surgical debridement.[42-44,55,67-70]
   d. Allograft of diaphyseal segments: in infected and non-infected bone losses, in losses greater than 3 cm, it can be combined with the first stage of the Masquelet technique, using the same way polymethylmethacrylate without or with antibiotic (gentamicin) plus 1 to 4 grams of powdered vancomycin per dose of cement, both in methyl methacrylate and in the soft tissues after surgical debridement, plus placement of the diamond mixture with collagen membrane (Pfizer gelfoam) at its ends as containment and scaffolding. The use of diaphyseal segment allograft will depend on previous surgeries, whether or not the patient has an available iliac crest, the patient's age, diet, and vitamin D determination.[1-5,9,46-48,50,55]
   e. Vascularized fibula grafting for infected or non-infected bone losses of up to 3 cm, can also be combined with the first phase of the Masquelet technique, using polymethylmethacrylate with or without antibiotics (gentamicin) plus 1 to 4 grams of vancomycin and application of a diamond concept mixture with collagen membrane (Pfizer Gelfoam).[56-59]
   f. Ilizarov bone transport for infected or non-infected bone losses greater than 7 cm, which can be combined with the first phase of the Masquelet technique.[60-64]

Material and methods

In October 2022, during the XXXII Mexican Congress of Orthopedics and Traumatology, efforts were initiated to create a proposal for the classification and algorithm in the management of bone losses. A consensus methodology was employed using a focal group comprising the authors of this article, all orthopedic and trauma medical specialists. The main author, as the moderator and proposer of the topic based on scientific literature, proposed the creation and characteristics of the classification and algorithm. The following proposal with conclusions obtained from the consensus was derived.

Proposal for classification and algorithm in the management of bone loss

A bone loss is an increasingly frequent challenge that we orthopedists face, so we have developed a simple classification and algorithm which will serve us in the treatment of the management of massive bone loss, whether infected or not. Velázquez-Moreno and Casiano-Guerrero, publish non-union treatment algorithm where they describe a therapeutic guide for diaphyseal non-union, which divides it into aseptic and septic and accordingly, if treatment is required to eradicate infection by debridement and scarification, take into account if there is bone contact, being atrophic or hypertrophic, both are treated with a locked nail, and only if it corresponds to atrophic, autologous or bank bone graft is applied. If the bone loss is less than 3 cm, it is treated with the placement of a locked nail plus a non-transferable external fixator, plus an autologous cancellous bone graft or a bone bank graft. If the loss exceeds 3 cm, it is treated through bone transportation, and in bone loss plus bone shortening, lengthening plus bone transportation can be used.[71] Ferreira et al, describe the management of tibial non-unions according to a new treatment algorithm, in case of chronic osteomyelitis with protocolized management and taking into account if there is no bone loss or defect if it is rigid hypertrophic the treatment with a circular fixator plus closed distraction and if there is a deformity, correction of the deformity, if it is mobile oligotrophic or atrophic, alignment, stabilization with circular fixator and bone graft, if it is mobile hypertrophic (pseudoarthrosis), resection of the same plus bone transport with fixator circular, in the case of bone defect, shortening of the limb with or without lengthening with circular fixator or bone transport with circular fixator.[72] Grunert et al, base their treatment on algorithms based on imaging diagnostics, both radiological and nuclear medicine, using contrasted dynamic magnetic resonance and an optimal therapeutic approach based on the widely known «diamond concept». However, regarding the size of the bone defect, they take into account less than 2 centimeters, perform spongy aplasty and greater than 2 centimeters, perform the Masquelet technique, segments-transport, or shortening, depending on each case to be treated.[73]

Currently, according to the algorithms available in the literature, Velázquez et al., although they take into account, performing debridement plus scarification, the size of the bone loss and the implant to be placed, centromedullary nailing only or more external fixators, transportation with or without bone lengthening, in terms of biology, they only mention placing autologous or bank bone graft. On the other hand, Ferreira et al, took into account the use of a circular fixator plus distraction, shortening with or without lengthening, bone transport and biologically only the bone graft. Grunert et al, although they carry out a therapeutic approach in the «diamond concept», they are based on radiological and nuclear medicine diagnostic imaging, using dynamic contrasted magnetic resonance, without establishing an order of therapeutic options (Masquelet technique, segments-transport and shortening) in losses greater than 2 centimeters.

Although these management algorithms take into account bone graft, autologous, and allograft, in general, it is necessary to specify in detail in an orderly manner, according to the size of the bone loss, the use of the orthobiological mixture based on the diamond concept, absorbable gelatin, the use of autologous tricortical iliac crest block, the induced membrane technique and the placement of allograft in the intercalary segment. The foregoing seems fundamentally useful to us, since on the one hand, currently the diamond concept has become indispensable for its use to optimize the biological environment and, on the other hand, the order of application of the best techniques available in the literature, according to the loss whether infected or not, according to the amount in centimeters of absence of bone we have, since the more bone loss, the less chance of success.

Therefore, it is essential to optimize the best biological, mechanical and surgical techniques described in the literature, taking into account first the surgical debridement and scarification. In terms of the application of the order of the different techniques and orthobiological options available, in first place the autograft with diamond orthobiological mixture, secondly, the induced membrane technique with diamond orthobiological mixture and thirdly, the use of allografts in intercalated segments. This is more likely to eradicate a bone infection if there is one, achieve bone consolidation and finally bone rescue, if possible, a complete functional integration of the patient, this being the final objective of the treatment.

The classification that we are proposing is based on the centimeters of bone loss and whether or not it is infected, and then establish a treatment guide according to the main orthobiological elements that we have within reach, such as bone marrow aspirate, bone marrow concentrate, bone marrow aspirate clot, platelet-rich plasma, demineralized bone matrix, autologous graft such as the iliac crest, bone allograft in chips or diaphyseal or complete segments, morphogenetic protein, as well as surgical techniques that can help us to achieve bone consolidation such as the preparation of the Giannoudis diamond mixture, use of absorbable gelatin, placement of an autologous block of the iliac crest, the induced membrane technique and the placement of bone grafts in diaphyseal or metaphysodiaphyseal intercalated segments, according to the experience in our osteoarticular rescue module of the orthopedics service of the General Hospital Dr. Miguel Silva and at the Memorial Hospital in Morelia, Mexico. There are other techniques that can be used if the aforementioned techniques have failed or depending on the case and surgeon's experience, such as the use and placement of vascularized fibula grafts and the Ilizarov bone transport *(Figure 6)*.

The classification is based on:

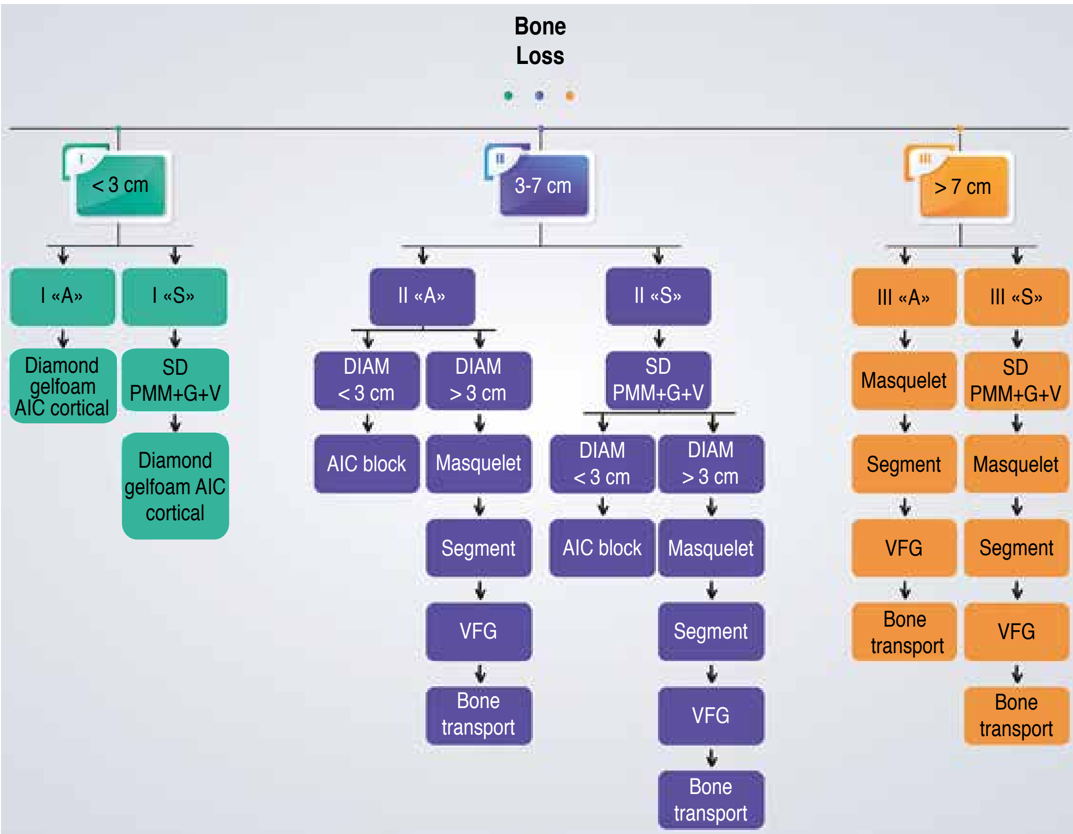

Figure 6: Classification and algorithm proposal for the orthobiological management of bone loss.
I = type I. II = type II. III = type III. Type I = bone loss less than 3 centimeters. Type II = bone loss of 3 to 7 centimeters. Type III = bone loss greater than 7 centimeters. «A» = aseptic or not infected. «S» = septic or infected. DIAMOND = diamond blend based on autologous iliac crest cancellous chips, allograft cancellous chips, platelet-rich plasma, bone marrow aspirate, bone marrow aspirate concentrate and demineralized bone matrix. GELFOAM = absorbable collagen sponge. AIC CORTICAL = autologous iliac crest cortex. SD = surgical debridement. PMM+G+V = polymethylmethacrylate plus gentamicin plus vancomycin. DIAM = diameter. AIC BLOCK = autologous iliac crest block. MASQUELET = induced membrane or Masquelet technique. SEGMENT = intercalary allograft segment. VFG = vascularized fibular graft. BONE TRANSPORT = bone transport Ilizarov.

1. Bone loss according to its size in centimeters:

Type I: less than 3 cm, type II: of 3 to 7 cm, type III: more than 7 cm.

1. Whether it is infected or not:
2. «A» if it is aseptic and «S» if it is septic.

It is worth mentioning that strict debridement and scarification are always required as the first step in any procedure that we will mention below until healthy bleeding tissue is achieved, that is, a sign of paprika is present.[23]

Loss less than 3 cm:

I «A»: bone loss of less than 3 cm without infection:

a. The orthobiological mixture is applied under the diamond concept in bone loss wrapped in absorbable collagen sponge (Gelfoam) and sometimes, according to the case, autologous iliac crest cortices can be placed as walls in the loss, all being wrapped by absorbable collagen sponge (Gelfoam).
b. Autologous iliac crest block and in the joints between the graft and the recipient bone, the application of orthobiological mixture under the diamond concept plus absorbable collagen sponge (Gelfoam).
c. Induced membrane with or without central absorbable collagen sponge and/or the periphery of the orthobiological mixture under the diamond concept.

I «S»: infected bone loss less than 3 cm:

a. Masquelet Phase I: polymethylmethacrylate with gentamicin is placed and 1 to 4 grams of vancomycin per dose of cement is added in both polymethylmethacrylate, bone, and soft tissues of the surgical approach, this is maintained for 3 to 4 months until there are no data both clinical and C-reactive protein, erythrocyte sedimentation rate and leukocytes at normal levels (acute phase reactants).
b. In a second surgical stage, the diamond mixture plus absorbable collagen sponge (Gelfoam) is placed in the periphery with or without autologous iliac crest cortical walls.

II «A»: bone loss of 3 to 7 cm without infection:

a. With a bone diameter of less than 3 cm: placement of an autologous iliac crest block and in the joints between the graft and the recipient bone, the application of orthobiological mixture under the diamond concept plus absorbable collagen sponge (Gelfoam).
b. With a bone diameter greater than 3 cm: induced membrane technique with or without central absorbable collagen sponge and/on the periphery of the mixture under the diamond concept.
c. With a bone diameter greater than 3 cm: placement of the allograft in the intercalary segment and in the joints between the graft and the recipient bone, the application of an orthobiological mixture under the concept of diamond plus absorbable collagen sponge (Gelfoam).
d. For bone diameter greater than 3 cm: placement of vascularized fibula and at the graft-to-receiver bone junctions, application of an orthobiological mixture using the diamond concept plus absorbable collagen sponge (Gelfoam).
e. For bone diameter greater than 3 cm: Ilizarov bone transport.

II «S»: bone loss of 3 to 7 cm infected:

a. Masquelet phase I: polymethylmethacrylate with gentamicin is placed and 1 to 4 grams of vancomycin per dose of cement is added in both polymethylmethacrylate, bone, and soft tissues of the surgical approach, this is maintained for 3 to 4 months until there are no data both clinical and C-reactive protein, erythrocyte sedimentation rate and leukocytes at normal levels (acute phase reactants).

In a second time:

a. With a bone diameter of less than 3 cm: placement of an autologous iliac crest block and in the joints between the graft and the recipient bone, the application of a mixture plus absorbable collagen sponge.
b. Phase II Masquelet induced membrane technique with or without central absorbable collagen sponge and/or on the periphery of the mixture.
c. With a bone diameter greater than 3 cm: placement of the allograft in the intercalary segment, and in the joints between the graft and the recipient bone, the application of a mixture plus absorbable collagen sponge (Gelfoam).
d. For bone diameter greater than 3 cm: placement of vascularized fibula and at the graft-to-receiver

bone junctions, application of an orthobiological mixture using the diamond concept plus absorbable collagen sponge (Gelfoam).

e. For bone diameter greater than 3 cm: Ilizarov bone transport.

III «A»: bone loss greater than 7 cm without infection:

a. Membrane technique induced with or without central and/or periphery absorbable collagen sponge of the orthobiological mixture under the diamond concept *(Figure 7)*.
b. Placement of allograft in the intercalary segment and in the junctions between the graft and the recipient bone, the application of an orthobiological mixture under the concept of diamond plus absorbable collagen sponge (Gelfoam).
c. Placement of vascularized fibula and at the graft-to-receiver bone junctions, application of an orthobiological mixture using the diamond concept plus absorbable collagen sponge (Gelfoam).
d. Ilizarov bone transport.

III «S»: bone loss greater than 7 cm infected:

a. Masquelet phase I: polymethylmethacrylate with gentamicin is placed and 1 to 4 grams of vancomycin per dose of cement is added in both polymethylmethacrylate, bone, and soft tissues of the surgical approach, this is maintained for 3 to 4 months until there are no data both clinical and C-reactive protein, erythrocyte sedimentation rate and leukocytes at normal levels (acute phase reactants).

In a second time:

a. Induced membrane technique with or without central and/or peripheral absorbable collagen gelatin (Gelfoam) of the orthobiological mixture under the diamond concept.
b. Placement of the allograft in the intercalary segment and in the joints between the graft and the recipient bone, the application of an orthobiological mixture under the concept of diamond plus absorbable collagen sponge (Gelfoam).
c. Placement of vascularized fibula and at the graft-to-receiver bone junctions, application of an orthobiological mixture using the diamond concept plus absorbable collagen sponge (Gelfoam).
d. Ilizarov bone transport.

Conclusions

We can avoid complications such as non-union in fractures with initial bone loss by anticipating the problem and applying the diamond concept from the beginning, giving it the essential biological contribution for bone healing. Septic or aseptic bone loss affects both the physical and mental health of patients. Many

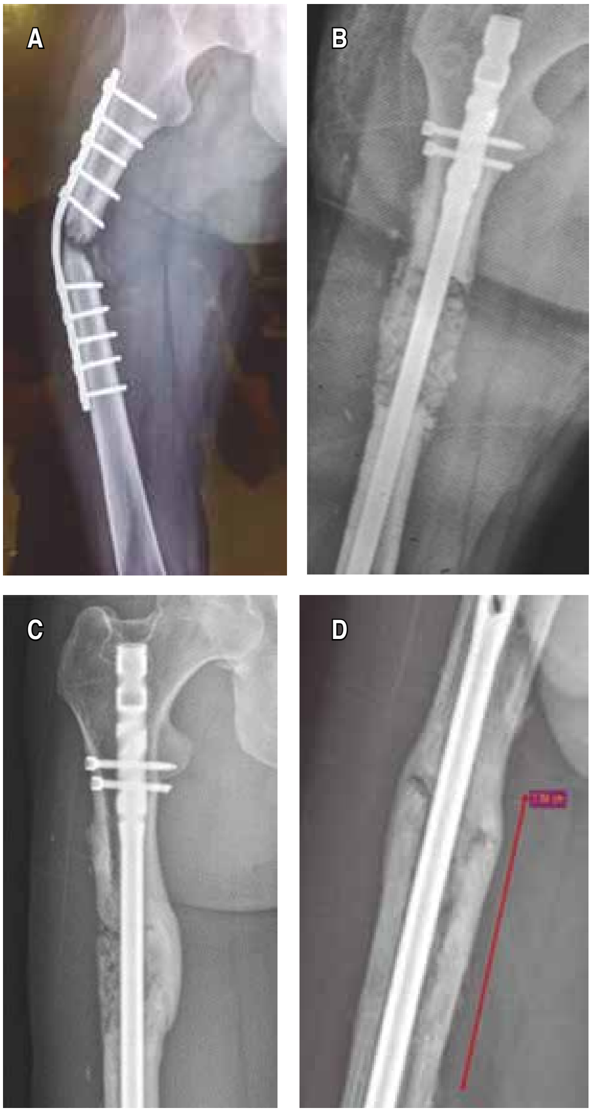

Figure 7: Type IIIA: **A)** Anteroposterior X-ray of femur shows bent plate with no union in proximal femur. **B)** Anteroposterior X-ray of femur with bone loss of 7.5 cm and with the composite graft and the universal femoral nail (Masquelet technique phase II). **C)** Anteroposterior X-ray of femur with 18 months of follow up after the Masquelet technique. **D)** Lateral X-ray of femur with 18 months of follow up after the Masquelet technique.

of these patients have undergone several previous surgeries and come to us to help them. Therefore, by having order through a treatment algorithm, based on the best scientific evidence available, such as the diamond concept, we are giving the importance to biology and to the mechanical stability, preventing complications by using orthobiologics if possible since the initial surgery on the patient based on the diamond concept using iliac crest autograft plus allograft chips, demineralized bone matrix, bone marrow aspirate, bone marrow concentrate, and platelet-rich plasma.

We have embodied these elements and techniques in the present proposal of a therapeutic algorithm for bone loss according to the quantity and whether they are infected or not, since based on this, we will have greater or lesser probabilities of achieving bone regeneration and expected functionality. The smaller the loss, the non-infected condition, and the more we can use orthobiological elements that together, based on the diamond concept, generate osteoinductive, osteoprogenitor and osteoconductive properties, the greater the chances of success. However, each time the complications and bone losses are greater, which is why we have to use all the elements and techniques that we have at our disposal and use them in order, optimizing these resources that we have depending on the size of the loss and if it is infected or not. When faced with bone loss, whether acute or chronic, in order to achieve bone salvage, given the scientific evidence, the current orthopedist has to optimize both the biological and mechanical environment, thus avoiding complications or solving them if they are already established.

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Conflict of interests

No conflict of interest is declared.