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New biograft solution, growth factors and bone regenerative approaches in neurosurgery, dentistry, and orthopedics: a review

N. MONTEMURRO[1], E. PIEROZZI[2], A.M. INCHINGOLO[3], B. PAHWA[4], A. DE CARLO[1], A. PALERMO[5], R. SCAROLA[3], G. DIPALMA[3], M. CORSALINI[3], A.D. INCHINGOLO[3], F. INCHINGOLO[3], B. RAPONE[3]

[1]Department of Neurosurgery, Azienda Ospedaliero Universitaria Pisana (AOUP), University of Pisa, Pisa, Italy
[2]Department of Dental and Maxillofacial Sciences, Sapienza University of Rome, Rome, Italy
[3]Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari, Italy
[4]University College of Medical Sciences and GTB Hospital, New Delhi, India
[5]College of Medicine and Dentistry, Birmingham, UK

Abstract. **Bone regeneration following surgery, trauma, or any other condition is an autologous process that can fail, necessitating the requirement of novel procedures and materials. Recently, significant progress has been made in the research related to regenerative medicine. At the same time, biomedical implants in spine surgery, orthopedics, and dentistry are facing many challenges and posing clinical concerns.**

A PubMed, MEDLINE, and Scopus review was carried out to identify all studies dealing with bone regenerative approaches in dentistry, orthopedics, and neurosurgery from database inception to December 2022.

There has been an upsurge in the implication of a multitude of materials in the enhancement of bone regeneration and/or neo-bone formation, including blood-derived growth factors, new biografts, biosynthetic polymers, inorganic compounds, and sea corals, in the very recent years. Stem cells (SCs) have been found to be efficacious and safe modalities in osteogenesis. Furthermore, bone regeneration/formation depends on the host's immune system and metabolic condition. Epidermal growth factors (EGFs) and their receptors (EGFRs) are important in the mechanism of wound repairing and healing through the recruitment of stromal stem cells for epidermal and dermal regeneration. Similarly, biocomposite developed from Silica assembled with calcium and phosphorous has been utilized in the treatment of broken bones.

In this review, we summarized the clinical and laboratory evidence of bone regenerative approaches in the field of spine surgery, orthopedics, and dentistry. An accurate pre-operative screening is the key to managing and carefully planning all surgical steps and achieving the final success.

Key Words:
Bone regeneration, Growth factors, Osteogenesis, Stem cells, Biocomposite, Neurosurgery, Dentistry.

Introduction

Bone width and height deficiencies can occur as a result of multiple inflammatory and traumatic conditions, non-healing fractures, metabolic disorders, systemic diseases, or chronic periodontal disease that may negatively affect either skeletal or tooth-supporting structures. Dental, spine, and orthopedic surgeons face a multitude of challenges in their daily practice which include atrophy due to prolonged dental wearing or prosthesis, rejection due to hyper-immune response, post-extraction defects with hyper-pneumatized sinuses, chronic implant inflammation with advanced bone resorption, trauma, misalignment and infections causing malfunction. Hence, there is a pressing need for novel techniques which are more effective and less invasive: split crest technique, autologous block bone grafts, intraoral bone grafts, heterologous bone grafts, and bioglass with resorbable or non-resorbable membrane and, titanium meshes[1-6]. The use of xenografts in bone grafts remains a very controversial topic since they may contribute to zoonotic transmission of diseases and graft rejection leading to devastating necrosis of deeper structures[7,8]. The utilization of titanium mesh is limited due to the "aseptic loos-

Corresponding Authors: Francesco Inchingolo, MD; e-mail: francesco.inchingolo@uniba.it
Biagio Rapone, DDS; e-mail: biagiorapone79@gmail.com

ening of titanium's particle", infection and eventually heightened immune response[9]. The outcome related to rejection from the use of titanium implants is similar in all types of surgical implant procedures, such as in cranioplasty, long bones hip replacements, and dentistry. The unrelenting inflammatory process starts at the implant-bone interface and is triggered by the recruitment of pro-inflammatory cells and molecules that intensify bone resorption mechanism[10]. Using bioengineering techniques, it is possible to design biomaterial scaffolds and tissue grafts to decrease the disadvantages linked to more conventional procedures. The main intent is to improve graft absorption by ameliorating the grade of osteogenicity, osteoconductivity, and osteoinductivity of the scaffold and host. The replacement of damaged tissues with an artificial prosthesis goes back to the past when archeologists excavated materials such as metals (gold and silver), shells, and corals that were used to replace broken/missing human bones[11]. Since bone tissue damage occasionally occurs due to accidental trauma and pathological causes, more than 2.2 million bone grafts are performed annually worldwide[12,13]. Currently, treatment protocols for bone tissue damage primarily focus on autologous and allogeneic grafts, with autologous grafts considered the gold standard[14]. However, using bone grafts to treat bone tissue damage is associated with several limitations, including the risk of developing an immune response, an inadequate supply of grafts, and donor site morbidity[15]. Regenerative medicine and tissue engineering have emerged in recent decades as promising approaches for the repair of bone tissue damage, with the goal of reducing the complications associated with conventional methods[15-17]. Biomaterials for bone tissue engineering can be described as impermanent matrices that provide a suitable microenvironment for cell proliferation and differentiation[13]. This study aims to review new techniques, materials, and new bioengineered products reported in the literature and assess their applications in the field of spine surgery, dentistry, and orthopedics.

Methods

A PubMed, MEDLINE, and Scopus review was conducted to identify all studies dealing with bone regenerative approaches in dentistry, orthopedics and neurosurgery. The following search terms were used from database inception to December 2022: bone AND/OR regenerative approaches in combination with neurosurgery AND/OR dentistry AND/OR orthopedics. A total of 1,397 articles, including those listed in the references of the retrieved studies, were found originally. We then excluded the following items: all publications not dealing with bone regenerative approaches in dentistry, orthopedics, and neurosurgery; all studies different from original articles (e.g., case report/case series, letters, commentaries, etc.); all preclinical studies; non-English written papers; and any other publication that did not comply with the goal of the present review. Further relevant references were identified from the bibliography of extracted articles as needed. After this process, a total of 74 studies were included in this review.

The Clinical Utility of Autologous Blood Derivate: CGFs, PRP, PRF, PB-SCs and Biografts

Different outcomes nowadays have demonstrated the rich functionality and support of blood derivatives like growth factors (GFs), Platelet Rich Plasma (PRP), platelet-rich fibrin (PRF), and stem cells (SCs) in combination with biografts which hold a huge potential for bone and soft tissue regeneration and reconstruction. Their morbidity is extremely low, making it a safe procedure. These derivatives promote bone growth, homeostasis, and vascularization[18-23]. The activity of GFs depends on the nature of the factor, the type of target cells, the functional status, and the site where the GF is located. In addition, the activity performed by a GF can be modified by other GFs or even by some cellular matrix proteins, acting either synergistically or antagonistically, which means that a GF can exert both a stimulatory and inhibitory effect.

PRP, Growth Factor Families, and Superfamilies

Platelets contain several molecules like the alpha-granules that are rich in GFs, such as the transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and Platelet-derived growth factors (PDGFs). These factors play a significant role in all phases of tissue healing by recruiting mesenchymal stem cells, as also during the synthesis of the extracellular matrix. The topical application of PRP showed to provide additional forms of exogenous GFs contributing to a faster healing and reconstructive process of the wound[24].

Transforming Growth Factors Beta

The TGF-beta family members are involved in embryonic growth and thus are responsible for stem cell differentiation, thereby playing a major role in immune regulation and, therefore, in the repairing process, inflammatory and cancer mechanisms[25-28].

Vascular Endothelial Growth Factors (VEGFs)

The activities of VEGFs are not limited to the vascular system but include regular physio-logical functions in bone and hematopoiesis, immunity responses, and wound healing, as well as in growth and development[28-35].

Platelet-Derived Growth Factors (PDGFs)

Outcomes from different studies[36-38] on PDGF receptor-α signaling showed their involvement in gastrulation and facial skeleton, hair follicles, spermatogenesis, central nervous system (CNS), lung development, and intestinal villi and skeleton, while PDGF receptor-β signaling pathway is crucial in the vascular system and early hematopoiesis.

Epidermal Growth Factors (EGFs)

EGFs and their receptors (EGFRs) are important in the mechanism of wound repairing and healing through the recruitment of stromal stem cells for epidermal and dermal regeneration. Currently, there is a high interest in the use of EGFs as part of novel therapeutic approaches in chronic non-healing wounds or abnormal scars such as scalds[39-42]. EGFR inhibitors (EGFRIs) can be used as therapeutic agents in the treatment of neoplastic insurgences. However, the chronic use of these inhibitors increases events of skin toxicity with papulopustular rash that eventually compromises wound healing[43-44].

Biomaterial for Scaffold and Grafts and Biomaterials Classification

The rationale of any bone biomaterial as a scaffold or graft is not only to substitute but restore the functionality of the replaced part physiologically and anatomically, ensuring complete biocompatibility without provoking rejection. An ideal grafting material is biocompatible, bioresorbable, and non-antigenic, easily accessible, does not loosen its inner integrity on sterilization, and is easy to manipulate. Additionally, these ideal substitutes should sustain osteoregeneration that includes: osteoconduction, osteoinduction, osteogenesis, and osseointegration[45,46]. Osseointegration refers to the ability of the implant to anchor to the host bone surface without causing the formation of fibrous tissue at the bone-implant interface; osteoconduction refers to the ability of the implant to act as three-dimensional physical support allowing the free homing of osteoprogenitor cells and start the process of bone formation. This is explicitly a process of invasion that allows starting of the calcium matrix deposit and vascular ingrowth within the implant; bone induction refers to the feature to provide biological stimulus to induce differentiation of undifferentiated pluripotent stem cells towards osteoblastic phenotype; osteogenesis refers to the ability to continue the differentiation process of host and "donor" progenitor cells to osteocells in charge of mineralized bone matrix formation[45-48].

Autologous

Autologous grafts or autografts are materials extracted from the same individual, generally taken from intraoral sites like symphysis of the mandibular ramus, the chin, the anterior maxillary nasal part, and the tuber; extraoral sites like the anterior and posterior iliac crest and the shank including the calvaria region. These sources represent the "gold standard" among all biomaterials with the highest level of safety and biocompatibility. Furthermore, the optimal presence of biocompatible and bioavailable bone morphogenetic protein (BMP) that favors bone induction makes these grafts the ideal material for sinus regeneration[49,50]. It should also be noted that bone grafts should be placed only in a site free from infections and/or inflammation. The bone graft healing process begins at the interface of grafted bone with the recipient site. The greater the area of the implant, the greater the grade of revascularization and the higher the available surface for bone progenitor cells to create contact. Stability of implants is essential in early bone formation without the right grade of stability, we may observe an abnormal repair that consists of fibrotic connective tissue. Depending on the site, the area, the volume and the degree of the damage, the surgical technique intended to be used, the autologous bone graft can be in different forms such as particulates, mono or bi-cortical osteotomies blocks, either alone or in combination with osteoconductive materials (mixed grafts). Particulates, either pure or mixed, are indicated in cases of sinus procedures, and block grafts are shown[51-53] to overcome vertical or transverse resorptions.

Allografts

Homologous allografts are materials from donors of the same species, the allografts may come from either living corpses or cadavers. Once the bone is removed, the material must undergo a deep process of cleaning to remove soft tissues, sterilization, and de-mineralization. In addition, these allografts, undergo a series of severe tests to ensure complete prevention against the risk of antigenicity and disease transmission. Once demineralized, the samples are frozen-dried and grinded into particles of 500 µm-5 mm (lyophilized), degreased with pure ethanol, and dehydrated. Subsequently, particles are further pressed to a final size of 250-750 µm (Demineralized Freeze-Dried Bone - DFDB)[54-56]. The recipient osteoclasts, while reabsorbing the inorganic part of the implant, expose the BMP contained in the organic matrix and simultaneously increase the local concentration of calcium and phosphorus, which are useful for the process of ossification. In this way, these grafts work primarily as an osteoconductive material and only in a later stage will perform as osteoinductive, always less than DFDBs[54-56]. In both cases, the osteoinductive qualities vary depending on the age of the body, the size of particles, and the site of samples[56].

Xenografts Derivate

Derived from different species, usually bovines and porcine, xenografts must undergo a series of tests and processes, including demineralization, sterilization, lyophilization, and freezing. Though extensively used, xenografts possess a similar osteoconductive activity and are relatively more convenient. Furthermore, their use reduces the need for a second surgery for bone harvesting[55,57,58]. However, xenografts have demonstrated a low capacity for inducing an adequate height and width in large defects, especially those of bovine origin.

Hydroxyapatite

Hydroxyapatite [Ca10P04(OH)2] is a bioinert material that chemically binds to bone without causing collaterals or rejection and inflammatory reactions. Hydroxyapatite is a non-toxic material and serves as a homing scaffold for osteogenic cell migration, cell growth, and development. The higher stability of hydroxyapatite compared to other calcium phosphates is probably the most attractive feature from a clinical perspective[59-62].

Bioglass Graft Materials

Biocomposite developed from Silica assembled with calcium and phosphorous has been utilized in the treatment of broken bones. The innovative aspect of this glass material resides in becoming a part of the surrounding tissues and their physiological molecular microenvironment, which is possible due to the induction of genes responsible for osteogenesis and growth factor production. This material has the capacity to bond to both bone and soft tissue[63-67].

Calcium Sulphate

Calcium sulphate (in the form of Plaster of Paris-POP) has been extensively used in both periodontal implantology and in orthopedics for bone regeneration owing to its high osteoconduction property that offers enough mechanical strength to be used as basic material[68,69]. An innovative approach was taken where 3D printed POP was produced at low temperature together with synthetic or biological type 1 collagen to enhance the biomechanical properties of the 3D scaffold while improving the osteoconduction and osteoinduction since Type 1 collagen plays a crucial role in the mineralization of bone tissue[70-73].

Fisiograft

Fisiograft has a molecular structure with a very high density, giving it the unique property of having a highly uniform resorption time. Over the period of 6 months, the scaffold increases the size of the damaged bone, consequently increasing the vascularization and circulation within the implant site[74].

Beta-Tricalcium Phosphate (ß-TCP)

This is a bioinert material with a good osteoconductive capacity which, once inserted into the recipient damaged site, undergoes reabsorption that is usually completed within a period of 6-9 months, completely replaced by new bone. It is particularly used in sinus lift procedures and small oral bone defection[74-76].

Pep-Gen P15

PEP-Gen P-15 is a novel material for bone regeneration consisting of natural inorganic bovine bone (ABM) and a synthetic peptide (P-15). This material is able to mimic the ability of collagen to create bonding, migration, and differentiation. Outcomes from an *in vivo* study by Butz et al[77] revealed a time-dependent efficacy of PepGen P-15 Putty. The healing mechanism was precise and histomorphometric results confirmed a newly formed bone tissue[77].

Porites Lutea Marine Coral

An interesting study[78] was performed to assess bone regeneration using a combination of sea coral (*Porites lutea* species) and autologous osteoblasts derived from rabbit femur bone marrow in post-traumatic patients with non-unions, accidents, and/or bone dysfunction. The overall outcomes showed that the healing process occurred faster in the study group (coral + osteocytes) as compared to the control group (coral alone) with a higher quality of bone tissue formation.

Autologous Tooth Graft

Tooth-derived bone grafts could be potential bone regenerating materials as these are rich in growth factors, BMPs, and non-collagenous proteins like osteopontin, sialoproteins, osterix, and osteocalcin with minimal risk of disease and infection[79-81].

Autologous Stem Cells in Regenerative Medicine and Bone Reconstruction Clinical Application

The human body is an exceptional source of multiple types of stem cells (SCs), including mesenchymal (MSCs), neural (NSCs), hematopoietic (HSCs), and embryonic (ESCs), which may differentiate into different cell phenotypes such as osteoblasts, chondrocytes, adipocytes, myocytes, cardiomyocytes, and neurons. A rationale exists for isolating and re-introducing endogenous peripheral blood stem cells (PB-SCs) for regenerative purposes. Immediately following the acute injury from hours to a few days, PB-SCs and the MSCs sub-group can modulate inflammatory responses both locally and systemically. This immune modulatory response takes place *via* two specific events: firstly, through the Macrophage-derived paracrine signaling molecules like the BMP2, Oncostatin M, and Prostaglandin E2 (PGE2); secondly, through the ability of MSCs to produce immune-modulatory cytokines and GFs such as TGF-β, and indoleamine 2,3-dioxygenase 1 (IDO). Additionally, within weeks after the traumatic event, the SCs start initiating the repairing mechanism by differentiating into specific osteocytes inducing the organization of local endogenous reconstructive molecules, factors, and cells[82-85]. The significance of interleukins, cytokines, and hormones in the re-vascularization, mineralization, and bone/cartilage re-modeling activity of hPB-SCs has been deeply elucidated, and their important role is fully appreciated as an external supporter in bone grafting therapy[86,87]. Aging and the general health of individuals strongly affect the status of circulatory and dormant SCs; patients affected by degenerative metabolic/neurological dysfunction such as type 2 diabetes, multiple sclerosis (MS) or chemotherapy revealed to have MSCs with a much higher rate of autophagy, reactive oxygen species (ROS) accumulation, mitochondria deterioration and therefore higher apoptosis[88-90].

Physiology of Bone Grafts in Regenerative Surgery

The main aim in surgical procedures using grafts with the support of autologous blood derivate is to induce and reach the closest level of body bone regenerative mechanism. The graft should enable the recipient to endogenous osteoinduction, osteoconduction, and osteogenesis with adequate vascularization within the implant and bone interface. An adequate mechanical stability of the graft or scaffold is also a critical point for bone healing and repair. Bone regeneration is composed of transitional phases where the formation of soft, fibrous connective tissues, cartilage, and woven bone, provide the mechanical stability that eventually leads to bone formation, supporting scaffold for cell and tissue differentiation. The mechanical loading affects the regeneration process, with different stress distributions favoring or inhibiting the differentiation of tissue phenotypes[91,92]. The mechanism of implantation follows the body repair process and can be summarized in 3 phases. The first one is immediately after the surgery, up to 4 days, an initial inflammatory response accompanies a formation of a blood clot around the graft. These early events are coordinated by platelets, presiding functions such as hemostasis and the release of mediator factors like PDGF, which favors angiogenesis; TGF-β, which favors maturation of pre-osteoblasts in osteoblasts and fibroblasts mitogenesis; insulin-like growth factors (IGF1/2), in charge of activating osteoblasts present at the endosteal level[93]. Neutrophils and macrophages, whose task is promoted by a decreased pH and low oxygen within the local microenvironment, enter to remove debris and necrotic debris. Macrophages are also involved in chemotaxis and mitogenesis. From day 5, there is a better and more uniform organization of the coagulation clot.

The endosteal and periosteal sources of pluripotent stem cells are recruited to start the initial regenerative process by factors such as BMP and TGF-β. Thanks to the stable structure offered by collagen fibrils, endogenous osteoblasts move in, and pluripotent MSCs start their differentiation into osteoblasts, and osteoid tissue is produced during the first 4 weeks. Starting from the second week, there is the withdrawal of inflammatory cells, increasing osteoclastic activity and necrotic debrides, and dead cells are cleaned by macrophages *via* phagocytosis. Meanwhile, blood vascularization of the graft takes place with higher recruitment of pluripotent MSCs from bone marrow (BM)[94-96]. The second phase is characterized by the remodeling and replacement of osteoid tissue with a lamellar bone through the bone osteoinduction mechanism regulated by factors like BMP, FGF, PDGF, insulin-like growth factor (IGF), interleukin (IL)-1, and IL-6[96], whereas the third phase is characterized by a proliferation of vascular capillaries to ensure constant nourishment even to more distant portions of the recipient site. At this stage, the graft acts as a structural support for both angiogenesis and subsequent bone osteoconduction[96,97].

Bone Regeneration Beyond a Classical View

The augmentation/implant ratio and the correct bone space and level of damage are important factors in implant survival. The use of blood derivatives like PRP, PRF, and autologous GFs channeled into qualitative autologous and allografts, with xenoderivate bovine/porcine, synthetic-like bio-scaffold such as β-TCP and bioglass have been reported in literature[98-101]. All these materials showed promising results in a wide variety of regenerative medicine applications, albeit with discordant results. To reach more conclusive and stable results, currently, the use of SCs coupled with PRP and PRF is being implicated. Though autologous grafts remain the golden standard, there is a practical constraint of supply along with the possibility of patient injury, infection, and morbidity, together with longer operation hours and high costs. Consequently, there is a great need for new systems for the regeneration of bones, both large and small sizes[98,100].

The healing process is also compromised with the use of non-autologous materials with lower osteogenetic and osteoinductive properties compared to autologous bone grafts; while the intermediate healing phase could remain unchanged, the time of revascularization and remodeling, reabsorption, and formation are not. For non-autologous materials, less remodeling time after the surgery and a great delay in revascularization have been reported[101,102].

The allogeneic bone grafts and biosynthetic materials may result in a deficiency in bioactive factors, and the whole compound of autologous blood derivate GFs, PRP, PPP, and PRF may also disclose some serious side effects. Consequently, there is a great need for new systems for the regeneration of bones, both large and small sizes[102]. The advance of new biological and engineering methods regarding bone regeneration started considering the cell-to-body intimately connected since progressive metabolic disorders are emerging conditions that negatively affect the endocrine/immune and regenerative cellular arrangements[88,89,101]. In this view, not only aging but the general health of individuals may eventually strongly affect the status of circulatory and dormant SCs. Patients affected by degenerative metabolic/neuro dysfunction, such as T2D or multiple sclerosis (MS), or patients who underwent special drugs or treatment like chemotherapy revealed to have MSCs with a much higher rate of autophagy, ROS accumulation and mitochondria deterioration and therefore higher apoptosis[88-90]. It has been suggested[89,90] that using SCs for regenerative medicine should be strictly scrutinized according to a consistent multi-disciplinary perspective.

Four weeks from the implant insertion, in the absence of complication, a first osteogenetic phase within the implant interface starts taking place like for autologous implants. However, for non-autologous materials, less remodeling was observed at 2 months postoperatively and a marked delay in revascularization at 8 months postoperatively[101].

A further concern is regarding the immune response to the implant, integration, or rejection. Rejection may happen in the early stage soon after the implant insertion or later, within a few days to 4 weeks from the surgery. Early-stage complications include infection, edema, ecchymoses and hematomas, emphysema, bleeding, flap dehiscence, and sensory disorders, while the late complications include perforation of the mucoperiosteum, edema, purulent exudate, swelling, pain on palpation, fistulae, maxillary sinusitis, mandibular fractures, failed osseointegration, bony defects, and periapical implant lesion[101,103]. A common challenge, whether autologous, al-

lograft, or biomaterial, is the presence of multiple pathogenic factors gathering at the graft/host bone interface[87-91].

Chronic complications are, in such cases, the most common episodes and are considered a consequence of malicious events occurring during surgery or during the postoperative period[104]. The main concerns in using implants, whether autologous, allograft, or biomaterial, are the presence of multiple pathogenic factors gathering at the graft/host bone interface. A compromised host defense mechanism is often a prerequisite for failure, rejection, and the presence of necrotic and traumatized bony tissue. It follows that a deep medical anamnesis of the candidate, his/her clinical history and familiar information, and a comprehensive blood test should be a prerequisite for the implant success[101,102,105-107]. Hence, the main factor to be considered for the choice of material is the time interval during which the biomaterial undergoes resorption. The resorption rate compatible with the host's endogenous formation rate is the most desirable outcome, probably, since the latter would not allow the formation of new bone within the neo-formed matrix. The phenomena of rapid resorption would inhibit revascularization and bone remodeling patterns, necessary to ensure osteoconduction and bone induction.

Limitations and Future Ahead

The courageous attempt to reproduce the complexity of natural developmental processes led to the formation of mature complete tissue. It follows that, while the adoption of mimicry approaches has eventually brought positive results, one should consider the interference of multiple variables such as physical, biochemical, metabolic, immunological, and hormonal conditions. There are huge differences between an inserted bone graft and a mature healthy tissue microenvironment but even more, there are crucial modifications between an inserted graft and the present health condition of the recipient[50,107-111]. Normal adult healthy development occurs under different immunological, inflammatory, hormonal, and metabolic settings, the complexity of these factors must be necessarily addressed if processes are to be tied together for a complete and successful integration of bone grafts and implants[112-120]. Endocrine signaling gradients which function in a healthy condition scale are likely to be subverted in a much-deteriorated situation. Modular implants, comprising those with smaller units, including GFs and cells, may be subjected to the internal unfavorable cellular and molecular microenvironment and may eventually be altered, leading to infection, necrosis, and eventually rejection.

The immune-endocrine-metabolic milieu, which modulates the entire process of regeneration, growth, and remodeling and adjusts the influx of cells, molecules, and GFs in healthy young and adult bone growth, remains to be fully elucidated. This is likely to be a crucial momentum if we are fully committed to unveiling the potential of the evolving bioengineering and regenerative medicine, as immune-endocrine-metabolic factors are significant mediators of bone healing and regrowth or, conversely, can result in retardation of healing if suppressed and neglected[86,87]. This last observation serves to highlight the differences between developmental processes underway during normal osteogenesis and those involved under post-traumatic graft induction. In fact, while inflammation, endocrine unbalances, and metabolic dysfunctions may represent part of the main drivers of bone decay and graft failures, they are completely functioning during normal bone development. Metabolic syndrome and correlated diseases like cardiovascular disease, DM2, osteoporosis and different degenerative condition of metabolic origin showed[107,121,122] a direct negative implication in skeleton homeostasis and bone turnover, but further studies are needed.

We have suggested a two-stage concept in bone regenerative therapy in this narrative overview. Current scientific studies in biomedicine, bioengineering, and regenerative medicine that combine to create a mechanical and technical answer for bone restoration decide the first level. This area of agreement covers a wide range of biomolecular techniques, including the diversity of graft resolutions to better respond to internal body stimuli, such as autologous GFs, PRP, and SCs, as well as the support of high-tech equipment to help surgeons and specialists improve the caliber of surgery and implant procedures, such as piezosurgery and lasers. Though we have advanced to a high level in bone repair and regeneration, the need for external intervention still exists, especially for patients for whom conventional bone grafting procedures ultimately proved ineffective. Basically, the second level of intervention includes and completes the first one. The external intervention focuses primarily on those internal abnormalities that impede the proper absorption of bone grafts and implants or lead to bone deterioration. The concept of restoring normal values would undoubtedly make a difference in better

graft results, whether in orthopedics, spine surgery, or dentistry, as the immune-endocrine-metabolic condition has shown to play a vital role.

Conclusions

Firstly, the kaleidoscope of biomolecular factors, such as the diversity of grafts consisting of autologous GFs, PRP, and SCs coupled with the support of hi-tech devices, facilitate surgeons and specialists to improve the grade of surgery and implant procedures, such as the piezosurgery and lasers. In recent years, highly efficient bio-scaffold solutions such as the Compact-bio BoneR have been used in conjunction with hormones, like testosterone, estrogen, progesterone, recombinant human erythropoietin (rhEPO) and vitamins like vitamin D, C, and K inducing synergistic effect in terms of new bone formation. Secondly, the immune-endocrine-metabolic conditions have been demonstrated to play a crucial role, therefore, the idea of restoring normal values would certainly make a difference in better outcomes of the grafts. The secret to managing and carefully planning all the surgical processes and final success is an accurate pre-operative screening. Hence, treating a patient's pre-existing metabolic, endocrine, or immunological condition may be a useful tool and a workable therapeutic approach for healing the bone defect. Human clinical regeneration techniques can undoubtedly be used once the harmful originative reasons have been identified. Addressing the pre-existence metabolic/endocrine/immune conditions of the patients may provide a valuable tool and a feasible therapeutic solution for bone defect healing. In this review, we summarized the clinical and laboratory evidence of bone regenerative approaches in the field of spine surgery, orthopedics, and dentistry. An accurate pre-operative screening is the key to managing and carefully planning all surgical steps and to achieve the final success.

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ORCID ID
Nicola Montemurro: 0000-0002-3686-8907
Angelo Michele Inchingolo: 0000-0003-0104-6337
Bhavya Pahwa: 0000-0002-4010-8951
Antonella De Carlo: 0000-0002-3006-8431
Andrea Palermo: 0000-0002-3288-490X
Gianna Dipalma: 0000-0002-5947-8987
Massimo Corsalini: 0000-0002-0521-1363
Alessio Danilo Inchingolo: 0000-0002-6366-1039
Francesco Inchingolo: 0000-0003-3797-5883
Biagio Rapone: 0000-0002-0062-6594

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