DOI: 10.15825/1995-1191-2025-2-112-126

THE USE OF AUTOLOGOUS BIOMATERIALS IN COMBINATION WITH BIOCOMPATIBLE MATRICES FOR RESTORATION OF BONE TISSUE DEFECTS (LITERATURE REVIEW)

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Bone defect repair is an interdisciplinary research field encompassing surgical orthopedics, regenerative medicine, tissue engineering, immunology (*addressing biocompatibility challenges*), materials science and technology (*including additive manufacturing, porosity, and mechanical strength*), and nanotechnology for developing biocompatible matrices that enhance bone regeneration. This literature review highlights recent advancements in bone tissue engineering, focusing on the application of autologous biomaterials in combination with biocompatible matrices to improve bone regeneration outcomes.

Keywords: bone tissue defects, bone marrow, peripheral blood, adipose tissue, autologous biomaterials, biocompatible matrices.

INTRODUCTION

Bone has the unique ability to fully restore its integrity after damage without fibrous tissue formation, retaining its original shape, size, and mechanical strength [1, 2]. Age-related pathology, immunodeficiency states, large areas of damage, and infectious complications can significantly reduce the regenerative potential of bone tissue. In such cases, bone restoration requires specialized methods and surgical techniques, along with a prolonged postoperative rehabilitation period [3]. Bone grafting (using autografts, allografts, and xenografts), along with biocompatible matrices (natural or synthetic) and metal/polymer implants, are currently standard approaches in surgical orthopedics for bone defect repair [3, 4]. Worldwide, approximately 2 million bone grafting procedures are performed annually, making bone tissue the second most frequently transplanted tissue after blood transfusion. Bone autografting is widely regarded as the gold standard for bone defect replacement [5]. However, this procedure has significant limitations, especially when dealing with large or multiple bone defects: limited donor site availability, increased surgical time & anesthesia requirements, and postoperative pain at the donor site [6]. An alternative strategy to traditional bone grafting is the application of regenerative medicine technologies, which use autologous cells and tissues combined with tissue engineering methods [7, 8]. This review explores the potential sources of autologous biomaterials that can be harvested in a hospital setting – bone tissue, bone marrow, peripheral blood, and adipose tissue – and examines their integration with biocompatible matrices to create *in situ* tissue-engineered constructs for bone defect replacement [7, 9].

TISSUE-ENGINEERED BONE CONSTRUCTS

The use of tissue-engineered constructs based on autologous biomaterials in combination with biocompatible matrices can serve as both a supplement to standard techniques and an independent method for bone defect replacement [9, 10].

A tissue-engineered construct for bone defect replacement is a triad that integrates three essential components for stimulating osteogenesis and new bone tissue formation: biocompatible matrix, growth factors, osteogenic cell populations (Fig. 1) [1, 9].

To fully restore bone tissue at the defect site, a tissue-engineered construct must exhibit the following key characteristics [1, 9]:

1. Osteoinduction – growth factor-mediated recruitment, proliferation, and differentiation of mesenchymal stem cells (MSCs) into osteogenic cell lines.

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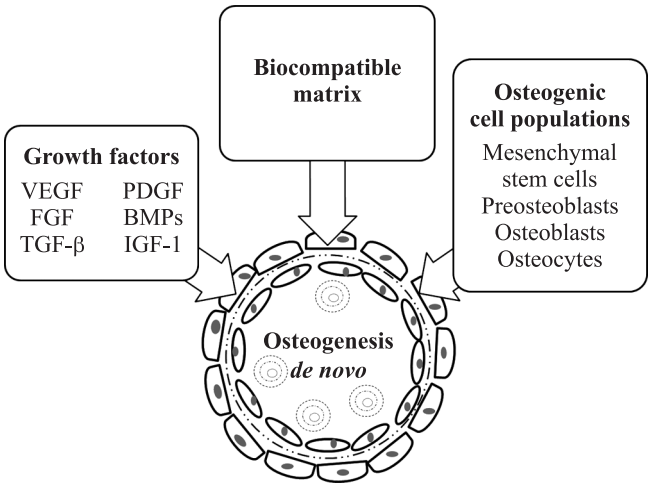

Fig. 1. Bone tissue engineering triad optimal for *de novo* bone formation

2. Osteogenesis – the process of *de novo* bone formation by osteogenic cells.
3. Osteoconduction – the ability to support bone formation across the entire construct surface by providing mechanical support for cell attachment and migration.
4. Osteointegration – the ability to bind seamlessly to adjacent bone without triggering aseptic inflammation or fibrous tissue formation.

AUTOLOGOUS BIOMATERIALS OBTAINED IN A CLINICAL HOSPITAL SETTING

Bone tissue

Bone tissue for autotransplantation is typically harvested from the iliac crest, long tubular bones, skull bones, or mandible [11]. Trabecular bone is known for its ideal osteoconductive characteristics and contains MSCs with high osteogenic potential [12]. The large surface area, due to its spongy structure, ensures high metabolic activity, facilitating the exchange of nutrients, biomolecules, and gases. This structural advantage enables rapid revascularization of the graft, typically occurring within 48 hours [13]. A cortical bone graft exhibits lower osteoconductive, osteoinductive, and osteogenic properties, but it compensates for this with higher mechanical strength [14]. A dense matrix in cortical bone grafts slows down revascularization, extending the process up to two months [15]. Vascularized bone grafts are among the most effective methods for bone defect replacement [16]. The material for transplantation in the form of a bone flap is typically harvested from the fibula, distal metaepiphysis of the femur, or distal metaepiphysis of the radius. The survival rate of these grafts is close to 100% [17, 18]. The difficulty of routine application of vascularized bone grafts arises from the need for microsurgical techniques, which require an operating microscope and special instruments [19, 20], as well as the duration of the operation and the high traumatization of the donor site [21].

Bone marrow

Numerous studies and clinical trials have demonstrated the safety and efficacy of using autologous bone marrow (BM) aspirate as a component of tissue-engineered constructs for bone tissue defect replacement [22]. BM-derived MSCs (BM-MSCs) have been shown to stimulate bone tissue regeneration [23]. BM-MSCs secrete growth factors that regulate chemotaxis, differentiation, proliferation, and secretory activity of bone cells, ultimately controlling physiological remodeling and healing of bone defects [24]. Thus, Bone marrow aspirate is an accessible and abundant source of cells that can be used in self-donor technologies for bone defect replacement [25].

Peripheral blood

Peripheral (venous) blood (PB) is used to isolate platelet-rich plasma (PRP) [26, 27]. PRP is rich in growth factors that can accelerate bone tissue regeneration [28, 29].

According to the classification proposed in 2009, platelet concentrates are divided into four main types based on their biological properties and mechanisms of action, which are determined by the concentration of platelets, leukocytes, and fibrin and, therefore, have different indications for clinical use. These types are:
– pure platelet-rich plasma (P-PRP);
– leukocyte- and platelet-rich plasma (L-PRP);
– pure platelet-rich fibrin (P-PRF);
– leukocyte- and platelet-rich fibrin (L-PRF) [30].

Pure platelet-rich plasma

In clinical practice, P-PRP can be used as either a liquid (injectable) form or a gel (fibrin glue) directly applied to the injury site [31]. Platelet lysate (PL) is derived from P-PRP through a process that involves successive cycles of freezing at –80 °C and rapid thawing at +37 °C. This process causes the destruction of platelet α-granules, which results in the release of numerous growth factors [32]. PL contains all known components found in human venous blood, promotes proliferation and migration of stem and progenitor cells due to the high content of platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), and several other and other bioactive substances (stromal cell factor-1/SDF-1, thrombospondin, P-selectin) [33]. PL has been shown to significantly enhance the proliferative activity of MSCs) and promote their differentiation into osteoblasts. The angiogenic factors released from PL stimulate the formation of new blood vessels [34]. PL can be stored at low temperatures for long periods

(up to 9 months), with full retention of its activity after thawing [35].

Leukocyte- and platelet-rich plasma

L-PRP, like P-PRP, can be prepared in either liquid form or as a gel [36]. L-PRP is widely used in cardiac surgery, operative gynecology, reconstructive surgery [37], traumatology and orthopedics, and sports medicine [38]. L-PRP has been shown to possess antibacterial properties, which can significantly accelerate wound healing [40]. Experimental studies, both *in vitro* and *in vivo*, have demonstrated that L-PRP promotes angiogenesis and osteogenesis at the site of bone tissue damage [41].

Pure platelet-rich fibrin

P-PRF is a fibrin-based biomaterial derived from whole blood without the addition of anticoagulants [42]. P-PRF has a dense consistency, and consists of two visible parts: yellow portion (main body with fibrin) and red portion (red blood cells) [43]. P-PRF contains numerous fibrin strands and is an ideal matrix for promoting the growth and differentiation of osteoblasts osteoblasts, fibroblasts and endothelial cells (Fig. 2) [44].

Concentrated P-PRF (C-PRF) exhibits a high osteogenic potential. C-PRF is an advanced form of P-PRF; the resulting fibrin clot is significantly larger, denser, and richer in growth factors compared to P-PRF [45].

Leukocyte- and platelet-rich fibrin

L-PRF has unique biological and mechanical properties, characterized by a dense fibrin network, enmeshed with platelets and leukocytes, which allows it to be used as a carrier for other cell types [46]. The L-PRF clot, when compressed between two layers of sterile gauze, forms a strong and resilient membrane that can be immediately used intraoperatively as a barrier membrane in bone defect repair [47, 48].

The combined use of PRP and various biocompatible matrices offers a safe, simple, and effective alternative to traditional autologous bone grafts in bone defect repair [49].

Adipose tissue

Adipose tissue is primarily composed of mature adipocytes making up over 90% of its volume, and a smaller heterogeneous fraction of cells collectively known as the stromal-vascular fraction (SVF) [50, 51]. The SVF contains various cell populations including preadipocytes, fibroblasts, immunocompetent cells, vascular smooth muscle cells, endothelial cells, and adipose tissue-derived MSCs (AD-MSCs) [52]. AD-MSCs secrete growth factors like FGF-2, VEGF, IGF-1, TGF-β1, PDGF, and BMP-2, which allows using these cells for *in situ* bone repair [53]. The safety and efficacy of AD-MSCs for bone tissue defect repair have been validated through numerous preclinical studies and clinical trials [54, 55].

EXAMPLES OF COMBINATION OF AUTOLOGOUS BIOMATERIALS WITH BIOCOMPATIBLE MATRICES FOR RESTORING BONE TISSUE DEFECTS (ANIMAL MODELS, CLINICAL USE)

Preclinical studies using animal models (*in vivo*) (Table 1) are essential for validating the effectiveness of bone tissue defect repair methods based on tissue engineering technologies [56].

An ideal animal model should closely mimic human physiology, biology, and biomechanics [88, 89]. Numerous studies have shown that small laboratory animals like mice, rats, and rabbits present challenges in adequately modeling extensive bone defects and their restoration in humans [89]. These models only partially reflect the diversity of processes involved in bone tissue

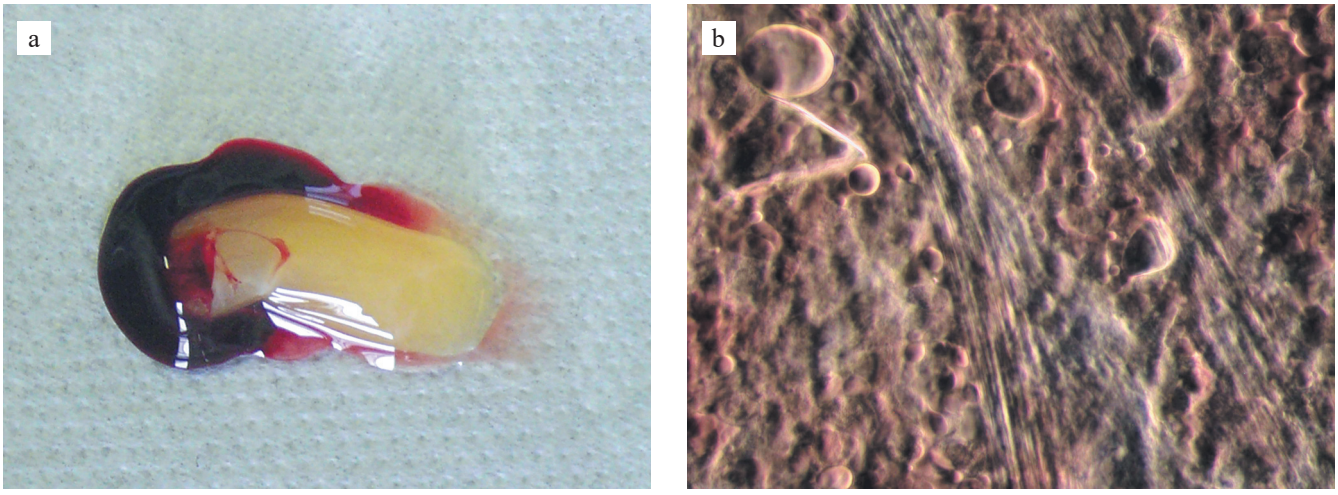

Fig. 2. Structure of fibrin clot (P-PRF): a, yellow part – main body with fibrin, red part – erythrocytes; b, microphotograph of fibrin filaments in the main body, hanging drop method, phase-contrast microscopy of native material, 100× magnification. Photographs from the authors's personal archive

regeneration in humans, making them less suitable for translational medicine research [56]. The advantage of large animals is that their immune systems are more similar to that of humans, which is particularly important when studying the role of immune factors in bone regeneration [90]. Large animals have a body mass and bone structure comparable to humans, allowing for the creation of large bone defects, the fixation of implants or prostheses, and the performance of surgical interventions that closely mimic real clinical conditions for bone integrity restoration in humans [91].

Currently, some methods for restoring damaged bone tissue using autologous biomaterials in combination with various biocompatible matrices are being introduced into clinical practice (Fig. 3) [92, 93].

The clinical results obtained confirm the efficacy of these methods, but scientific publications on this topic are limited to reports of single cases or cases with small groups of patients (Table 2) [93].

PROSPECTS FOR THE USE OF SKELETAL BONES IN COMBAT-RELATED TRAUMATIC INJURY

The enormous kinetic energy of modern munitions causes multiple extensive tissue and organ damage [115]. Studies indicate that limb injuries in approximately 75% of the wounded are the result of mine blast wounds (Fig. 4) [116].

Bone injuries in such wounds are characterized by multiple comminuted fractures, often with the formation of extensive defects (Fig. 5) [116, 118].

Treating military personnel with combat injuries, especially those involving skeletal bones, is a critical and urgent task for the military medical service of the Russian Armed Forces [115, 119, 120]. The Ilizarov compression-distraction osteosynthesis method has traditionally been the only effective treatment for extensive bone defects [121]. However, Russian researchers have proposed an innovative alternative involving intramedullary osteosynthesis using transplantation combined

Table 1

Preclinical *in vivo* animal models of bone defects

Animal models	Anatomical localization of bone defects – composition of tissue-engineered construct – animal count
Rat	cranial vault – BM-MSCs (*xenogeneic, human) + poly-L-lactic acid (PLLA) – 9 individuals [57] cranial vault – BM-MSCs + chitosan + alginate + hydroxyapatite (Hap) – 6 individuals [58]. cranial vault – BM-MSCs + β-tricalcium phosphate (β-TCP) – 9 individuals [59] cranial vault – BM-MSCs + alginate + PLLA – 8 individuals [60] cranial vault – BM-MSCs (*xenogeneic, murine) + PRP + polyvinyl alcohol (PVA) + chitosan + silk fibroin + polycaprolactone (PCL) + β-TCF – 12 individuals [61] cranial vault – BM-MSCs + nano-HAp (nHAp) + gelatin – 5 individuals [62] femur – BM-MSCs (*allogeneic, rat) + (70% PLA + 30% PCL) – 8 individuals [63]
Rabbit	femur – BM-MSCs + PRF + biphasic calcium phosphate (BCP/80% β-TCP + 20% HAp) – 6 individuals [64] femur – PRF + DPC (40% β-TCP and 60% HAp) – 6 individuals [65] radius – BM-MSCs (*allogeneic, rabbit) + PRF + BCP (40% β-TCP + 60% HAp) + PVA – 9 individuals [66] radius – BM-MSCs + PLA + HAp – 9 individuals [67]
Sheep	tibia – BM-MSCs (*allogeneic, sheep) + PCL + HAp – 8 individuals [68] tibia – BM-MSCs + HAp – 4 individuals [69] tibia – BM-MSCs + (20% PLLA + 80% PCL) – 4 individuals [70] tibia – BM-MSCs (*allogeneic, sheep) + PCL – 8 individuals [71] tibia – PRP + PCL + β-TCP – 8 individuals [72] mandible – L-PRF + PLGA – 6 individuals [73] femur – carbon nanotubes + HAp + LPRF – 4 individuals [74] femur – AD-MSCs + β-TCP – 4 individuals (castrated rams) [75] metatarsus – AD-MSCs + autologous bone + nHAp – 6 individuals [76]
Goat	tibia – BM-MSCs + β-TCP – 6 individuals [77]
Pig	mandible – AD-MSCs (*allogeneic, porcine) + β-TCP + PLGA – 7 individuals [78] femur – PRF + BCP (40% β-TCP + 60% HAp) – 4 individuals [79] tibia – BM-MSCs + PRP + α-TCP – 8 individuals [80] tibia – AD-MSCs (*xenogeneic, human) + TCP – 1 individual [81]
Dog	femur – PRP + BCP (40% β-TCP + 60% HAp) – 8 individuals [82] mandible – AD-MSCs + PCL + β-TCP – 3 individuals [83] mandible – BM-MSCs + PCL + β-TCP – 3 individuals [83]
Monkey	femur – BM-MSCs + β-TCP – 7 individuals [84]

* – use of xenogeneic and allogeneic biomaterial as an alternative source. BM-MSCs, bone marrow-derived mesenchymal stem cell; nano-HAp or nHAp, nano-hydroxyapatite; PRF, pure platelet-rich fibrin; P-PRF, pure platelet-rich fibrin; L-PRF, leucocyte and platelet-rich fibrin; PRP, platelet-rich plasma; PLGA, poly(lactic-co-glycolic acid); AD-MSCs, adipose-derived mesenchymal stem cells.

with the transplantation of autologous bone tissue and a collagen-based biocompatible matrix. This approach enables the successful reconstruction of bone defects up to 12 cm in length and offers significant improvements

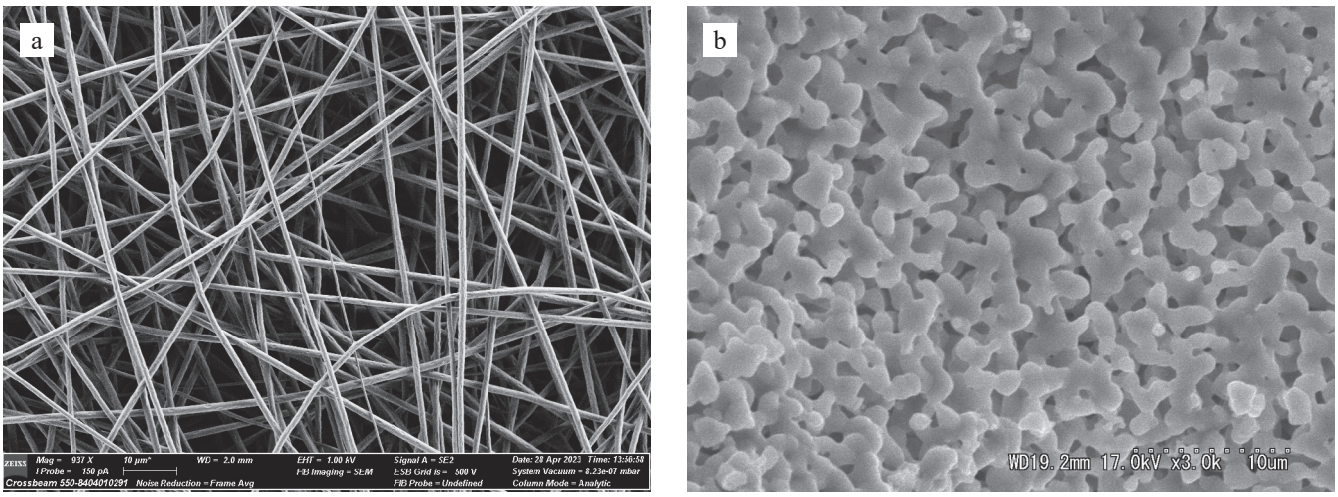

Fig. 3. SEM micrographs of some of the most commonly used biocompatible porous matrices in clinical practice. a, porous polylactide (PLA) matrix, obtained by electrospinning with the formation of a system of open and interconnected pores (average fiber diameter 800 nm, average pore diameter in the fiber 70 nm); b, matrix based on β-TCP, β-TCP granules contain multiple micropores with sizes ranging from 100 to 400 μm, total matrix porosity 75%

Table 2

Use of autologous biomaterials in combination with biocompatible matrices in clinical practice

Anatomical localization of bone defects	Composition of tissue-engineered construct	Patient count	Literature source
Cranial vault	Autologous bone + AD-MSCs + P-PRP (gel)	1	[94]
	AD-MSCs + β-TCP	2	[95]
	BM-MSCs (*allogeneic, donor) + β-TCP + PLLA mesh membrane	3	[96]
Maxilla	Autologous bone + BCP (40% β-TCP + 60% HAp)	27	[97]
	AD-MSCs + β-TCP	1	[98]
	BM-MSCs + β-TCP	3	[99]
	AD-MSCs + PRF + *Allogeneic bone	1	[100]
	AD-MSCs + carbonate apatite (CO_3Ap)	10	[101]
Mandible	AD-MSCs + β-TCP	23	[102]
	BM-MSCs + BCP (80% β-TCP + 20% HAp)	11	[103]
	Autologous bone + L-PRF	22	[104]
Mandible and maxilla	PRF + bioactive glass 45S5 (45% SiO_2, 24.5% Na_2O, 24.5% CaO, 6% P_2O_5)	20	[105]
Humerus	BM-MSCs + β-TCP + collagen sponge	1	[106]
Femur	BM-MSCs + β-TCP	9	[107]
Femur and tibia	Personalized 3D printed tubular mesh structures consisting of PCL (80%) + β-TCP (20%) filled with autologous bone in combination with HAp (40%) + calcium sulfate (60%) + gentamicin sulfate.	4	[108]
	Autologous bone + bioactive glass S53P4 (53% SiO_2, 23% NaO, 20% CaO, 4% P_2O_5)	13	[109]
Tibia	BM-MSCs + β-TCP	16	[110]
	Autologous bone + β-TCP	1	[111]
	Autologous bone + P-PRF (fibrin clot)	1	[112]
Bone defects of various localizations	Bone marrow aspirate + HAp (27 patients) Bone marrow aspirate + collagen sponge (12 patients)	39	[113]
	BM-MSCs + β-TCP	42	[114]

* – use as an alternative source of allogeneic biomaterial. BM-MSCs, bone marrow-derived mesenchymal stem cell; HAp, тфтщhydroxyapatite; PRF, pure platelet-rich fibrin; P-PRF, pure platelet-rich fibrin; L-PRF, leucocyte and platelet-rich fibrin; P-PRP, pure platelet-rich plasma; AD-MSCs, adipose-derived mesenchymal stem cells.

in both anatomical and functional outcomes, while also reducing the incidence of complications compared to the classical Ilizarov technique [9].The induced membrane (IM) method, proposed by French orthopedic surgeon Alain-Charles Masquelet in 2000 (Masquelet method), has become widespread and is actively used in clinical practice [122]. Bone defect repair using this method is performed in two stages. In the first stage, a cylindrical spacer made of polymethylmethacrylate is implanted into the defect site. This spacer mechanically isolates the defect from surrounding tissues, preserves a cavity for the subsequent placement of osteogenic biomaterials, and prevents fibrous tissue formation. Outside, a capsule of granulation tissue (the result of reaction to the foreign body) is formed around the spacer – this is the IM, which contains numerous collagen fibers, blood vessels, osteoprogenitor cells, immune cells (macrophages, lymphocytes), multinucleated foreign-body giant cells, osteoclasts. In the second stage, the spacer is removed, and the encapsulated space is filled with autologous bone graft or a biocompatible matrix. Within this space delimited by IM, revascularization of the graft and new bone formation occur [123]. The average interval between the two stages is approximately 22 months, while bone regeneration at the graft site typically takes 8–10 months. This technique allows for the restoration of bone defects ranging from 4 to 25 cm in length [124, 125].

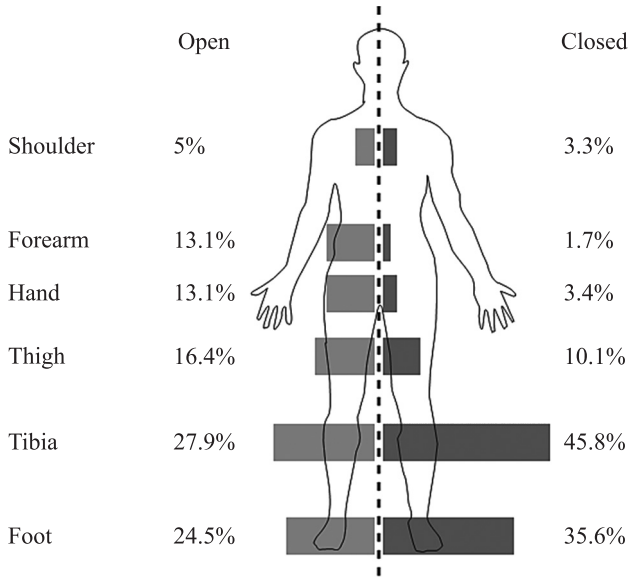

Fig. 4. Anatomical localization of skeletal injuries in an explosion [117]

The IM technique does not require complex equipment or advanced microsurgical skills, as is necessary with vascularized bone grafts. Its relative simplicity makes it especially valuable in military orthopedic surgery, particularly in scenarios involving active combat and limited medical resources [125].

It should be noted that there is no universal method that would be suitable for all wounded patients with bone defects. Each case requires an individualized treatment approach tailored to the specific clinical circumstances [126]. Servicemen with combat-related skeletal injuries represent a valuable human resource for our country's

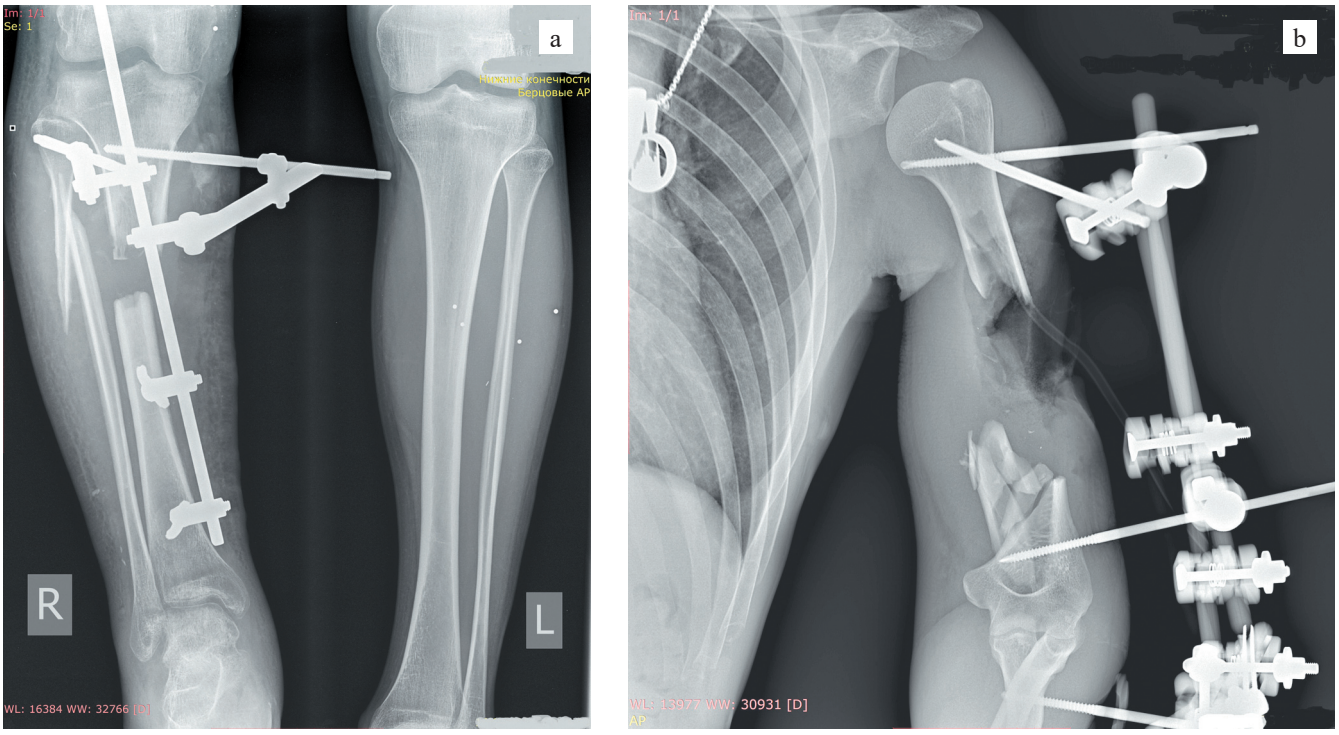

Fig. 5. Bone defects in mine blast injuries: a, right diaphyseal tibial defect, fracture of the right fibula in the upper third with displacement of the fragments, fixed with an external fixation device (EFD); b, soft tissue defect and left humerus defect in the middle third, fixed with an EFD device. Photographs from the authors's personal archive

Armed Forces. Successful treatment and rehabilitation of these individuals enable the return of experienced and battle-tested soldiers to active duty [127].

CONCLUSION

Methods utilizing autologous biomaterials with minimal *ex vivo* manipulation, combined with biocompatible matrices, have demonstrated effectiveness in restoring bone tissue defects across various fields, including orthopedics, traumatology, and dentistry. However, despite significant scientific and technical advancements and promising preclinical research, few of these approaches have transitioned into routine clinical practice. This gap between extensive research and real-world application highlights key challenges, including the scalability and cost-effectiveness of biocompatible matrices, as well as the need for standardized protocols for autologous biomaterial production.

The work was carried out within the framework of the State assignment National Research Centre "Kurchatov Institute" and Supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement 075-10-2021-093).

The authors declare no conflict of interest.

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The article was submitted to the journal on 9.07.2024