REVIEW ARTICLE

Periosteum: Functional Anatomy and Clinical Application

Azeez Omoniyi Adeoye[1], Siti Nurma Hanim Hadie[1], Ismail Munajat[2], Nur Izni Mohd Zaharri[3], Muhamad Syahrul Fitri Zawawi[4], Sharifah Emilia Tuan Sharif[5], Abdul Razak Sulaiman[2]

[1] Department of Anatomy, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia.
[2] Department of Orthopaedic, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia.
[3] Animal Research and Service Center (ARASC), Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia.
[4] Tissue Bank Unit, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia.
[5] Department of Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia

ABSTRACT

Periosteum is a connective tissue that envelopes the outer surface of bones and is tightly bound to the underlying bone by Sharpey's fibers. It is composed of two layers, the outer fibrous layer and the inner cambium layer. The periosteum is densely vascularised and contains an osteoprogenitor niche that serves as a repository for bone-forming cells, which makes it an essential bone-regenerating tissue and has immensely contributed to fracture healing. Due to the high vascularity of inner cambium layer of the periosteum, periosteal transplantation has been widely used in the management of bone defects and fracture by orthopedic surgeons. Nevertheless, the use of periosteal graft in the management of bone defect is limited due to its contracted nature after being harvested. This review summarizes the current state of knowledge about the structure of periosteum, and how periosteal transplantation have been used in clinical practices, with special reference on its expansion.
Malaysian Journal of Medicine and Health Sciences (2023) 19(3):362-374. doi:10.47836/mjmhs18.5.46

Keywords: Periosteal transplantation, Fracture healing, Periosteum, Periosteal expansion

Corresponding Author:
Abdul Razak Sulaiman, MMed (Ortho)
Email: abdrazak@usm.my
Tel: +609-7676000

INTRODUCTION

Bone tissue is vital for the sustenance of the body system. Apart from providing the support and protection for organs and soft tissue, it also serves as a spot of blood cells formation and acts as a source of production for both calcium and phosphate. Endosteum (i.e., a membrane that lines the interior cavity of the bones) and periosteum (i.e., connective tissue that envelopes the outer surface of the bones) plays important roles in bone growth, fracture recovery and bone reconstruction as they contain cells that are essential for bone growth and remodeling, namely osteoblasts, osteoclasts, and osteoprogenitor cells (1,2). The endosteum is composed of a layer of flattened osteoprogenitor cells and type-III collagenous fibres, which is also known as reticular fibres (2). While periosteum is composed of two layers; the outer fibrous layer and the inner cambium layer (3); and it is tightly bound to the underlying bone by Sharpey's fibers.

The outer fibrous layer of periosteum is subdivided into a superficial vascular, and a deep fibroblastic layer (4). While, the inner cambium layer of periosteum, known as the osteogenic layer, is composed of osteoprogenitor cells, namely fibroblast-like cells and osteoblast (5). Although osteoblasts are not present in the inner cambium layer of periosteum of mature bones, these cells emerge when they are needed, such as in fracture healing (1).

During the bone development and homeostasis, the cells in the periosteum contribute to bone thickening and cortical maintenance, whereas the growth plate plays a crucial role in longitudinal bone extension (4). Given these facts, the periosteum has shown to be a comparable source of cells for tissue engineering and regenerative medicine in clinical orthopedics. The periosteal graft transplantation has been reported to be useful in the management of complicated bone defects, such as delayed union and nonunion of fractures (6,7), and congenital nonunion pseudarthrosis of the tibia (CPT) (8). It has also been reported to stimulate

revascularization of bone allograft (9).

Meanwhile, the use of periosteal graft to treat bone defects have been limited by its contractile nature after being harvested from donor sites (8, 10). Since periosteal graft is usually needed in large size to fill in bone defects, there is a need for its size to be restored following its harvest and optimizing the method of transfer to recipient site. Therefore, this review highlights the general structure of periosteum, the methods of periosteal graft transfer, the clinical application of periosteal graft including methods of its transfer, limitations of its use in clinical practice, and possible solution to the problems.

FUNCTIONAL ANATOMY OF PERIOSTEUM

The simple gross morphological appearance of periosteum contradicts its complex histomorphology features as a composite double-layer framework of connective tissue that provides physical protection for the bone. As a dense irregular connective tissue, the outer fibrous layer of periosteum contains significant amount of collagen fibers including fibroblast and its progenitor cells. The collagen fibers of periosteum are mainly aligned with the bone surface (11). This structure contributes to the tensile strength of periosteum, as described in a phenomenon known as 'strain stabilization' (i.e., collagen fibrils that are perpendicular to the tensile load direction deteriorates more quickly than fibrils that are parallel to the loading direction) (11).

On the other hand, the inner cambium layer contains periosteal derived cells (PDCs), which consist of mostly fibroblasts, osteoblasts, mesenchymal stem cells (MSCs), mast cells, and pericytes (2). There is considerable heterogeneity among periosteal cells and matrix linked with the species, sex, age, embryonic origin, and the site or location of the periosteum due to changes in the nature of dynamic mechanical and biochemical settings (12).

The structure of periosteum is distinctly divided into three zones that have specific morphology and composition (13). Zone 1 is mostly composed of osteoblasts, with minimal amount of collagen fibrils. Zone 2 is dominated by fibroblasts and endothelial cells. Whilst, in Zone 3, there are abundant collagen fibrils and fibroblasts. These three zones have different fibroblast morphologies (13). With these compositions, periosteum acts as a sensor to mechanical loading, a source for osteogenic cells for bone formation and repair, and a reservoir for molecules that are essential for signaling (14).

BLOOD SUPPLY OF PERIOSTEUM

The periosteum receives its blood supply from four vascular systems, namely the intrinsic periosteal system, periosteocortical anastomoses, musculoperiosteal system, and the fascioperiosteal system (15,16). The intrinsic periosteal system is located between the inner cambium and outer fibrous layers. Based on the pattern of its arrangement, it could be subdivided into three: numerous short and small vessels that run without specific direction; vessels arranged in a circular pattern encircling the bone; and longitudinally arranged vessels running parallel to bone long axis (15,16). The periosteocortical anastomoses, also known as cortico-capillary anastomoses is formed by branches of periosteal arterioles that anastomose with the medullary arterial system near to Haversian canal at the external one-third of the cortical part of the bone (16). This arrangement reveals a clear connection between the nutritional artery and the periosteal blood flow (16). Meanwhile, the musculoperiosteal system forms strong connections with the surrounding muscles, which becomes dominant in condition when there is poor intrinsic periosteal blood flow (15,17). On the other hand, the fascioperiosteal system comprises of many segmental arteries, which vary between bones, due to the differences in fascia and muscles insertions (16). The blood supply of periosteum is illustrated in Fig 1.

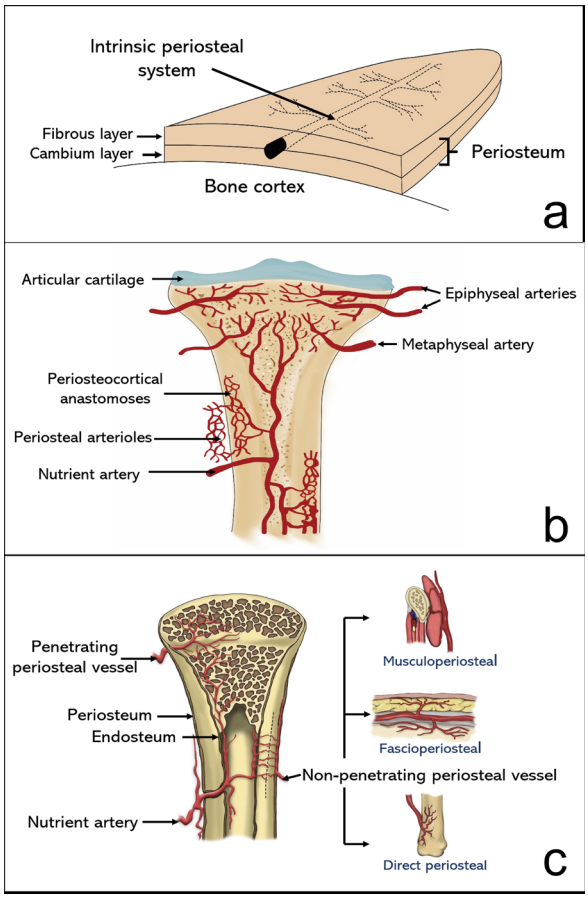

Figure 1: Blood supply of periosteum. (a) Intrinsic periosteal system located within the outer fibrous and inner cambium layers. (b) Periosteocortical anastomoses involve direct connection between of periosteal blood supply with nutritional artery. (c) Musculoperiosteal and fascioperiosteal arterial systems demonstrate blood supply to fascia and muscles

INNERVATION OF PERIOSTEUM AND NEURAL CONTROL OF BONE GROWTH

Inman and Saunders (18) reported that early studies found that direct, noxious mechanical stimulus of the periosteum caused painful perceptions in human. It was also reported that pain from bone is typically not perceived except if the periosteum is involved (19). The periosteum is innervated by both small diameter, slower conducting nociceptors; and large diameter, faster conducting encapsulated nerve endings (19).

The nervous system influences the bone metabolism via central regulation of bone cell actions The adrenergic sympathetic nervous system regulates the mechanism of bone formation and resorption primarily via ß2-adrenergic receptors (AdB2R) in the appendicular and axial skeletons (20). In vivo studies revealed that activation of AdB2R induced up-regulation of receptor activator of nuclear factor kappa beta (RANKL), an important mediator responsible for bone resorption (21). Nerve growth factors (NGF) and Semaphorin3a (Sema3a) are attractant and repulsive molecules respectively that are involved in bone metabolism (22,23). For instance, activation of NGF stimulates differentiation of osteoblast in mouse calvarium and promotes callus maturation and mineral apposition (24,25). Besides, bone mass stimulation is moderated by action of Sema3a, which enhances osteoblast and inhibits osteoclast differentiations (26).

FACTORS INFLUENCING PERIOSTEAL MORPHOLOGY AND OSTEOGENIC POTENTIAL

There are several factors affecting periosteal morphology, namely age, sex, species, and location. The age-related differences of periosteum include the number of periosteal fibroblast and osteoblast, vascular density, periosteal thickness, and collagen synthesis ability (27). The inner cambium layer becomes gradually thinner with age; hence, it is more difficult to distinguish the inner cambium from the outer fibrous layers of the periosteum in an adult compared to a child (28). Likewise, the number of periosteal fibroblasts and the density of blood vessels diminish with age (4). A previous study revealed that the cambium and fibrous layers of periosteum of adult rats are well vascularised; while in mature rats, blood vessels are mostly found in the fibrous layer (29). Indeed, PDCs of elderly person have strong growth potential and differentiation capability, but their ability to differentiate into chondrogenic and adipogenic lineages decreases with age (10). Nevertheless, the periosteum's regeneration abilities appear to be unaffected by age (14).

Besides that, the osteological potential of periosteum is influenced by various factors. For instance, the cranium had the largest osteogenic potential, followed by the ilium, radius, and mandible (14). Likewise, it was reported that osteogenic activity of the periosteal cells is higher in flat than in long bones (30). Besides that, the mechanical properties of periosteum differ between metaphyseal and diaphyseal areas, as well as between periosteum extracted from the anterior, medial, lateral, and posterior portions of a long bones (31). It was also reported that periosteum of calvaria demonstrated less osteogenic capacity than the periosteum of tibia, when non-vascularised periosteal grafts were used (32).

In addition, there is also sex-related difference of periosteum. For instance, parathyroid hormone (PTH) and oestrogen have been reported to stimulate the proliferation and death of PDCs of various sex origins (33). In general, androgens were demonstrated to increase the rate of periosteal bone growth (34). Periosteum in males expands due to androgens, with no change in endocortical diameter, resulting in increased cortical width; while, in females, the periosteal expansion stops, and endocortical bone production occurs, resulting in decreased medullary diameter. Insulin-like growth factor 1 plays a role in the regulation of periosteal apposition throughout puberty, especially when combined with sex steroids (35).

ROLES OF PERIOSTEUM IN NORMAL BONE GROWTH AND REMODELING

Bone grows in length or width. The bone lengthening is caused by chondrocytes that are present in the proliferative and hypertrophic zones of the growth plate (36). While periosteal apposition—a process through which mineralised tissue is added to outer bone surface by osteoblast—is responsible for bones to widen (37). In pediatric medicine, there is greater emphasis on bone growth in length; and thus, body height, when compared to bone growth in width; despite the vital roles bone growth in width plays in skeletal development (38). It is argued that increase in the length of the bone without simultaneous increase in width, the bone would become unstable and subsequently break (36).

There are several factors that coordinate the intricate bone longitudinal growth process, namely local, mechanical and systemic factors. Periosteum contributes to bone growth by acting as a constraint that causes compression on growth plate axis. When the periosteum is excised, this constraint is released, resulting in increased longitudinal growth in the growing skeleton (39).

Some studies conducted on the long tubular bones, indicated that the partial resection of periosteum lead to bone growth (40). A previous study that investigated limb discrepancy caused by a half-circumferential removal of periosteum in four-week-old chickens reported an observable difference at the angle between the diaphysis and metaphysis of distal tibiotarsus bone (39). Likewise, circumferential resection of periosteum

beneath the epiphyseal plate of tibia was observed to result significant bone growth in uniform and continuous manner (40).

Recent study confirmed that Osteocrin (OSTN), generated by periosteal osteoblasts, controls the growth plate expansion by promoting C-type natriuretic peptide (CNP)-dependent chondrocyte proliferation and maturation (41,42). OSTN functions as a mechanotransducer, participating in the regulation of long bone growth induced by mechanical loading (41). It was previously reported that overexpression of OSTN in transgenic mice increases bone length by increasing chondrocyte proliferation and maturation mediated by CNP signaling (43).

Besides that, periosteum is involved in bone remodeling as demonstrated in several animal studies (4,31, 43, 44). According to a study by Yiannakopoulos et al (45), apart from its biological function, periosteum offers mechanical aid for the bone, whereby mechanical loading on periosteal surfaces promotes bone formation. A study by Hagino et al., (46) revealed that PTH and mechanical loading at the periosteum of the tension surface of rat tibia induced a synergistic rise in the bone formation rate. In another recent study involving the use of Teriparatide (TPTD), an analog of PTH, bone formation was observed in the tension zone at the endocortical level and in the compression zone at the periosteal level (47).

In fracture healing, vascularity plays an important role by acting as a dynamic force responsible to cause intramembranous and endochondral ossification. The revascularisation process during fracture healing is explained by two theories: the centripetal and centrifugal flow models (48). While the centripetal flow model or "outside-in '' model, describes blood flows from the periosteum to the fracture site (49). The centrifugal flow or "inside-out" model describes that fracture revascularization is contributed by the intramedullary blood supply (50).

PERIOSTEAL GRAFT IN PROMOTING FRACTURE HEALING AND BONE FORMATION IN ANIMAL STUDIES

Periosteal transplantation is a surgical procedure used for the treatment of cartilage and bone defects. A periosteal graft is a highly vascular graft with a large supply of pluripotent cells, and thus has a high potential for regeneration (51). Periosteal autograft and allograft involve transfer of periosteum from one site to another in the same individual and different individuals of same species respectively, while periosteal xenograft involves periosteal transplantation between two different species (52, 53, 54).

Several studies demonstrated the importance of periosteal autologous transplantation in fracture healing and bone formation (52, 55, 56). Periosteal graft is usually placed on bare bone, and it can be transplanted either with attached blood vessels (vascularised) or without blood vessels (non-vascularised) (57). The use of the vascularised periosteum to enhance healing and bone graft integration has been demonstrated in previous studies (53, 58) Apart from the preservation of its vascular supply, ossification of the transplanted vascularised periosteal graft is also influenced by its capacity to collaborate with the recipient bed (58).

Likewise, the non-vascularised periosteal graft transplantation also showed significant bone formation in several experimental studies (60-63). These studies proved that healing occurred following the non-vascularised periosteal graft transplantation on the bone fracture of rabbit femur, which was created together with destruction of periosteum, endosteum and bone medullary cavity (63).

Besides that, previous research reported the osteogenic potential of periosteal allografts in fracture healing (64, 65). It was observed that significant bone formation happened following the implantation of periosteal allografts into muscle (54). On the other hand, Hoffman and Benoit (65) revealed that decellularized periosteal allograft transplantation on a femoral defect model showed no graft-mediated callus formation, minimal host integration, and no graft remodeling or remodeling due to lack of periosteal tissue. Meanwhile, xenogeneic periosteal transplantation has been proven to have stimulated the osteogenic and chondrogenic capacities of recipients' bone in a previous animal study. Ueno et al. (66) reported that human mandibular periosteal derived cultures on a collagen scaffold, which was grafted on cranial defects of Sprague Dawley mice, had resulted in significant bone formation. Nevertheless, both allogeneic and xenogeneic periosteal transplantation have numerous disadvantages, namely immunological turndown, disease transfer, high infection rate, delayed bone healing, pathological calcification of cartilage, as well as bone diseases following poor metabolism (67).

Experimental studies also demonstrated the construction of vascularised tissue engineered bone in vivo using rabbit model (68, 69). The studies involved the use of vascularised tibial periosteum and saphenous vascular bundle as the main components of in vivo bioreactor; beta-tricalcium phosphate (β-TCP) acted as scaffolds and were implanted into the bioreactor (68). Conclusively, vascularisation and osteogenesis were achieved as a result of the combination of vascularised periosteum, β-TCP as scaffold and vascular pedicle implantation (68). Likewise, the use of bioreactor approach on sheep model to reconstruct mandibular defect has also been reported (70).

PERIOSTEAL TRANSPLANT IN CLINICAL STUDIES

Given the proven efficacy of fracture healing in animal models, autologous periosteal transplantation has been applied in clinical practice (71, 72). For instance, application of autologous tibial periosteal transplantation in acetabuloplasty for the management of articular cartilage defect of hip bone has been proven reliable and effective (72).

A previous study by Soldado et al., (73) described the potential of vascularised tibial periosteal graft (VTPG) to effectively heal complicated nonunion and the ability to prevent nonunion of allograft for the treatment of nonunion in pediatric patients. Likewise, osteogenic potential of vascularised thumb metacarpal periosteal pedicled flap (VTMPF) was described in the management of adult patients with severe nonunion of the scaphoid (74). In a recent study, the non-vascularised periosteal graft harvested from medial condyle of femur is effective in healing the on metacarpal nonunion with weak bone neovascularization (75).

The adoption of vascularised tibial periosteal grafts has recently been recorded as a dynamic means of achieving bone union in Congenital Pseudoarthrosis of Tibia (CPT), a nonunion that occurred in fracture of dysplastic bone (76). Its fast ability to provide union in CPT, making it a better option when compared to formerly utilized techniques (76). Non-vascularised periosteal graft has been shown to provide union in CPT when it is use in combination with bone grafting, and intramedullary (IM) nailing of both the tibia and the fibula, in connection with Ilizarov fixation (8). The most serious complication regarding the method described by Thabet is refracture after CPT healing; it is usually required to adjust the position of the IM rod for restoration of ankle joint function. Liu et al., (77) reported high rate of healing after telescopic intramedullary rod was used in combination with surgery for the treatment of CPT in children. The clinical application of periosteal graft is summarised in Table I.

PERIOSTEAL TISSUE EXPANDER

One of the main limitation of periosteal graft transfer is the limitation in its size as a donor tissue. Thabet et al., (8) reported the shrinkage of a rectangular-shaped periosteal graft after-it was harvested from the medial aspect of the ilium. The periosteum was returned to its initial size with the aid of skin graft mesher, which could expand soft tissue to the maximum available size. The periosteal tissue expander and its function are illustrated is shown in Fig. 2.

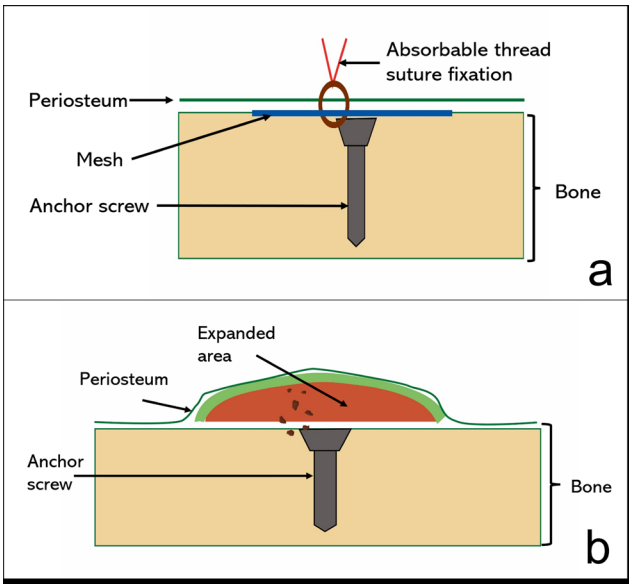

Figure 2: Periosteal tissue expander. (a) Initial position of the mesher and periosteum before expansion. (b) Final position of mesher and Periosteum after expansion

Table I: Studies on clinical application of periosteal grafts

Periosteal graft type	Application /indication	Result/Outcomes	Limitations /complications
Vascularised fibular periosteal graft	Management of bone union in children (71)	It aided bone union and promote healing	One case (out of 12 cases) of pedicled torsion was detected
Non-vascularised tibia periosteal graft	Repair of articular cartilage defects within hip joint, acetabuloplasty treatment (72)	Improves range of movement and walking tolerability, reduces hip pains. Suitable for management of acetabuloplasty	No complication reported in Non-vascularised tibia periosteal graft group
Vascularized tibial periosteal graft	Management of complex bone nonunion and allograft-host junction nonunion in children (73)	It was quick and highly successful for complicated bone nonunion, prevent allograft nonunion	In a patient with substantial comorbidities, the flap failed. There were no complications at donor sites
	Treatment of CPT (76)	Via the formation of a periosteal callus, bone union was achieved, and the flap survived	There were no union failures
Vascularized thumb metacarpal periosteal pedicled flap	Treatment of scaphoid nonunion in adults (74)	Adults who used this graft for severe scaphoid nonunion experienced good overall results.	No postoperative complications
Periosteal medial femoral condyle free flap	Treatment of metacarpal nonunion with impaired bone vascularization (75)	An efficient and biomimetic method of bone repair is provided by the graft	No postoperative problem
Non-vascularised iliac periosteal graft	Treatment of CPT (8)	Treatment for CPT that combines non-vascularized iliac periosteal graft, bone grafting, IM nailing, and Ilizarov fixation proved to be an appropriate alternative	Refractures occur in 8 of the 20 patients

CPT: congenital pseudarthrosis of the tibia

There are several studies that have highlighted the importance of expanding the periosteum through soft tissue expander (78-81). Results obtained from previous experimental studies supported that soft tissue augmentation can be induced intraoperatively by osmotic soft tissue expansion. The slowly expanding periosteum formed new bone around the expanding periphery, and the additional soft tissue formed served to cover the bone graft (79).

Tissue expansion is a method of expanding soft tissue that maintains its normal color, texture, thickness, and sensation with minimal scarring. A small donor area would be able to supply relatively bigger tissue after expansion (81). The commonly used soft tissue expander (STE) in previous experimental and clinical studies consisted of an osmotically active hydrogel, vinylpyrrolidone and methyl methacrylate, enclosed in a perforated silicone sheath. The initial size of the hydrogel was 2.5x7.5x3.0 mm and the size after maximum inflation was 5.6x11x6.0 mm. The number and size of holes in the surrounding silicone case regulates the speed of expansion (78,80).

In a previous clinical study that assessed the effects of internal soft tissue expander via evaluation of local bone graft, periosteal hydrogel expansion has been shown to be an appropriate way to obtain excess soft tissue to cover bone grafts, although further technical improvement may be needed to reduce difficulties, especially in patients who smoke (80). Another study verified that osmotic soft tissue expansion generates excess periosteum and soft tissue, and new bone can be produced beneath the titanium mesh using autologous bone graft or protein-free bovine bone mineral (82). Rupture, hematoma, infection and failure at the time of expansion are among the complications that were reported to be linked to soft tissue expansion (83-84).

The dire demand for soft tissue enlargement in the oral region has led to the manufacture of more advanced expanders (80). Previously used STEs are covered by a perforated silicone sheath with a flat tip for fixation (85). The outer sheath is specific to second-generation STEs, which, unlike the first-generation, lack such a membrane and enable self-inflating osmotic expansion (85). STEs have been used in previous experimental studies where they have been reported to result in bone resorption (86) and bone apposition (78, 82).

Despite the effectiveness evidence of STEs in promoting bone healing; its application in clinical practice is complicated and technically challenging, as it is time consuming, costly, and it resulted in pain and discomfort during the filling process of the expander (83,84). Aside from the previously mentioned disadvantages, researchers proclaimed that soft tissue expander can also affect the underlying tissue by causing bone resorption (86,87).

USAGE OF PERIOSTEUM TRANSPLANT ON BONE ALLOGRAFT SURGERY

Bone allograft is usually used to replace bone defects due to its size and shape, but it usually resulted in junctional nonunion and bone fracture (88). The utilisation of periosteal transplantation on allograft surgery have been reported in several experimental and clinical studies (53,89-91). Karaoglu et al (89) demonstrated that demineralized deep-frozen allograft covered with non-vascularised periosteum resulted in rapid and high quality ossification it was reported that bone allograft wrapped with non-vascularised periosteal graft have similar efficacy with standard treatment using autogenous bone graft transfer for the repair of bone defects in rabbits (90). Likewise, a study by Santić et al. (57) revealed better bone healing in tibial defect of rabbits that were treated with allogenous bone graft covered with vascularised periosteal graft, compared to their counterparts that received allogenous bone graft with non-vascularised periosteal graft (85). In a recent experimental study using rat model, vascularised periosteal graft was reported to promote allograft-host bone union, revascularization, and allograft bone regeneration, which takes place via intramembranous ossification (9).

Likewise, the ability of vascularised periosteal grafts to enhance union between the host bone and allograft in clinical cases has been reported (71). Besides promoting allograft-host bone union, vascularised periosteal graft also initiate revascularisation in a necrotic bone (91). The non-vascularised periosteal graft harvesting process and its use in allograft surgery are shown in Fig 3.

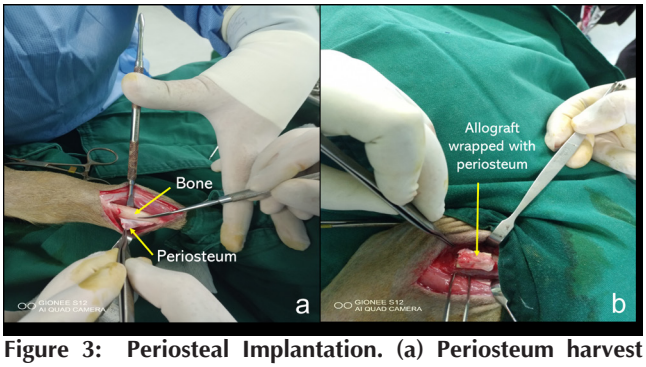

Figure 3: Periosteal Implantation. (a) Periosteum harvest from tibia donor bone. (b) Allograft wrapped with Periosteum at femur recipient bone.

PERIOSTEUM AND TISSUE ENGINEERING IN THE MANAGEMENT OF BONE DEFECT

Besides using the actual periosteum in the form of graft for the management of bone defects, an artificial periosteum can also be created via tissue engineering. Tissue engineering of periosteum involves in vitro growing of seed cells and placing them on a scaffold (92). In bone defect, the scaffold material containing

growth factors is implanted. As the scaffold material is fully absorbed by the body, the seed cells form new bone tissue with normal physiological framework and activities, and thus fulfilling the goal of bone defect repair (93).

The tissue engineered periostea have been reported for its effectiveness in the enhancement of osteogenesis (93). Nakahara et al (94) performed in vivo studies by exploring the periosteum derived progenitor cells (PDPCs) from young chicks' bones using tissue engineering procedures, with the conclusion that periosteum possessed osteogenic and chondrogenic potentials. These PDPCs may provide the best source of cells for tissue engineering, which will depend on availability, capability to rapidly undergo proliferation, as well as differentiation to numerous mesenchymal origins (95). It is important to note that the periosteum satisfies the three primary conditions for tissue engineering, namely a cell font, a scaffold for cell maintenance and distribution, and local growth factors source (96). Therefore, the exploration and optimization of the factors that control the osteogenesis and chondrogenesis of PDPCs will be of great benefit.

Despite the emergence of tissue engineering in regenerative medicine, limited clinical studies have concentrated on how periosteal grafts may be generated using tissue engineering procedures (92,97). It was also reported that there are insufficient studies that revealed the conditions of the periosteum important components like vascular niche and osteoprogenitor cells, especially in terms of their re-establishment (54). Hassibi et al. (98) investigated the impact of decellularized allogeneic bone graft enhanced by periosteal stem cells (PSCs) and growth factors on the bone reconstruction process using rabbit model. They concluded that PSCs implantation, when combined with growth factors as well as allogeneic cortical bone graft will serve as a compelling treatment for the reconstruction of large bone defects (99). Likewise, Baldwin et al. (54) carried out similar research that utilized stem cells that mimic the polyphasic morphology of the periosteum. This aim was achieved by combining a star-shaped polyethylene-glycol (starPEG) heparin hydrogel system loaded with human umbilical vein endothelial cells (HUVEC), medical-grade poly (ε-caprolactone) (mPCL) tubular scaffold seeded with human bone marrow mesenchymal stem cells (BM- MSCs).

Overall, the results suggest that human tissue-engineered periosteum constructs (hTEPCs) have successfully resynthesized osteoclastogenesis and the vascular niche of the native periosteum, and the presented live xenograft model provides a suitable in vivo environment for the evaluation of scaffold-based tissue engineering concepts that exploit human cells. Although tissue engineering is costly and requires advanced facilities, the use of tissue engineering in periosteal graft transfer is pertinent, as this will provide solution to the limited donor site and will produce large composite and scaffold (100).

PERIOSTEUM TRANSPLANT IN TREATING CARTILAGE DEFECT

Several studies have reported the abilities of the periosteal graft to reconstruct articular cartilage defects (55,101-103). Unlike in mosaic chondroplasty, where the treatment depends on unused cartilage, the utilization of autologous periosteal grafting makes use of its capacity to form new cartilage (103). Autologous non-vascularised periosteal graft has been proven to be an optional treatment for fixing articular cartilage (104). It was reported that cartilage reconstruction through the non-vascularised periosteum occurred primarily via endochondral mechanisms (105, 106). Likewise, the use of vascularised periosteal graft in cartilage reconstruction carries the possibility of subsequent ossification (105). The mechanism on how periosteum may contribute to cartilage repair is illustrated in Fig 4.

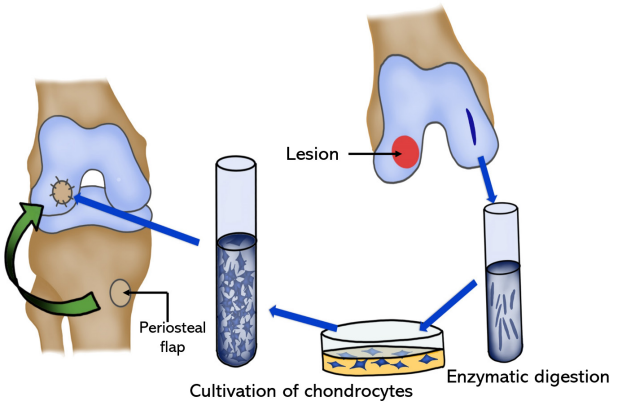

Figure 4: Mosaicplasty procedures for repair of cartilage defects

Periosteal graft transplantation has also played crucial roles in reconstruction of osteochondral defects (55, 104). Nevertheless, there is an increasing debate with regards to the orientation and placement of the periosteal graft, whether the graft faces the subchondral bone or joint (107). For instance, when a non-vascularised periosteal graft harvested from tibia was transplanted on osteochondral defects with the cambium layer facing the subchondral bone, the graft was able to successfully repair the defect revealing its chondrogenic potential (55). On contrary, O'Driscoll et al (108) who performed a study to compare two different placement approaches of non-vascularised periosteal graft, reported better cartilage formation when the graft was placed with cambium layer facing the joint compared to facing the subchondral bone. Nevertheless, Jaroma & Ritsilᴧ (109) found no significant difference in the cartilage formation regardless of the placement approach of the non-vascularised graft (i.e. either sutured facing the subchondral bone or facing the joint).

Although some researchers have reported success in achieving cartilage regeneration following a periosteal graft transfer, majority of these studies were limited to the regeneration of hyaline cartilage in the knee joint using the periosteum of tibia (110, 111). The periosteum possesses chondrogenic capacity when the environment is conducive for chondrogenesis to take place (112). For example, previous research by Yang et al., (113) showed that MSCs undergo chondrogenic differentiation in vitro by providing additional biological micro-molecules, namely bone morphogenetic proteins (BMPs), growth factors, Wingless-related integration site (Wnt) glycoproteins and matrix proteins. Ito et al (114) reported that chondrocyte precursors are found in the inner cambium layer of periosteum, the commencement of chondrogenesis is from the juxta osseous region of cambium layer to juxta fibrous region, adding that new cartilage growth takes place away from fibrous layer via displacement by readily formed cartilaginous tissue.

CONCLUSION

Periosteum provides a significant portion of blood supply to the bone and supports oppositional bone growth as well as contributing to remodeling of bone deformity. The ability of transferred periosteum to form bone has been utilised to promote union of bone and improve allograft incorporation, and this ability depends on the vascularity of cambium layer as described by the periosteal usage in focal cartilage defect. Hence, transplantation of vascularised periosteum provides better bone formation compared to non-vascularised periosteal graft. Nevertheless, the process of non-vascularised periosteal graft transfer is technically easier compared to vascularised periosteal graft transfer. Unfortunately, the non-vascularised periosteal graft is often shrunken following its harvest, and this limitation could be overcome with tissue expansion techniques. Further experimental and translational investigations are needed to estimate the efficacy of non-vascularised periosteal graft in the management of bone fracture.

ACKNOWLEDGEMENTS

This review is funded by the Universiti Sains Malaysia, Research University Grant (1001/PPSP/8012291).

REFERENCES

1. Bahney CS, Zondervan RL, Allison P, Theologis A, Ashley JW, Ahn J, et al. Cellular biology of fracture healing. J Orthop Res. 2019;37(1):35-50. doi: 10.1002/jor.24170
2. Allen MR, Hock JM, Burr DB. Periosteum: biology, regulation, and response to osteoporosis therapies. Bone. 2004;35(5):1003-12. doi: 10.1016/j.bone.2004.07.014.
3. Nahian A, Chauhan PR. Histology, Periosteum and Endosteum. 2022 May 8. In: StatPearls Aaron JE. Periosteal Sharpey's fibers: a novel bone matrix regulatory system? Front Endocrinol 2012; 3:98. doi: 10.3389/fendo.2012.00098..
4. Dwek JR. The periosteum: what is it, where is it, and what mimics it in its absence? Skeletal Radiol. 2010;39(4):319-23. doi: 10.1007/s00256-009-0849-9.
5. Bakri K, Shin AY, Moran SL. The Vascularised Medial Femoral Corticoperiosteal Flap for Reconstruction of Bony Defects within the Upper and Lower Extremities. Semin Plast Surg. 2008;22(3):228-33. doi: 10.1055/s-2008-1081405.
6. Wang T, Zhang X, Bikle DD. Osteogenic Differentiation of Periosteal Cells During Fracture Healing. J Cell Physiol. 2017;232(5):913-921. doi: 10.1002/jcp.25641.
7. Wang T, Zhang X, Bikle DD. Osteogenic Differentiation of Periosteal Cells During Fracture Healing. J Cell Physiol. 2017;232(5):913-921. doi: 10.1002/jcp.25641.
8. Thabet AM, Paley D, Kocaoglu M, Eralp L, Herzenberg JE, Ergin ON. Periosteal grafting for congenital pseudarthrosis of the tibia: a preliminary report. Clin Orthop Relat Res. 2008;466(12):2981-94. doi: 10.1007/s11999-008-0556-1.
9. Gallardo-Calero I, Barrera-Ochoa S, Manzanares MC, Sallent A, Vicente M, Lypez-Fernández A, et al. Vascularised Periosteal Flaps Accelerate Osteointegration and Revascularization of Allografts in Rats. Clin Orthop Relat Res. 2019;477(4):741-755. doi: 10.1097/CORR.0000000000000400.
10. O'Driscoll SW, Fitzsimmons JS. The role of periosteum in cartilage repair. Clin Orthop Relat Res. 2001;(391 Suppl): S190-207. doi: 10.1097/00003086-200110001-00019.
11. Foolen J, van Donkelaar C, Nowlan N, Murphy P, Huiskes R, Ito K. Collagen orientation in periosteum and perichondrium is aligned with preferential directions of tissue growth. J Orthop Res. 2008;26(9):1263-8. doi: 10.1002/jor.20586.
12. Matsushima S, Isogai N, Jacquet R, Lowder E, Tokui T, Lan- dis WJ. The nature and role of periosteum in bone and cartilage regeneration. Cells Tissues Organs. 2011; 194:320-5. doi: 10.1159/000324642
13. Squier CA, Ghoneim S, Kremenak CR. Ultrastructure of the periosteum from membrane bone. J Anat 1990; 171:233–9. PMID: 2081707 PMCID: PMC1257144
14. Li C, Fennessy P. The periosteum: a simple tissue with many faces, with special reference to the antler-lineage periostea. Biol Direct. 2021;16(1):17. doi: 10.1186/s13062-021-00310-w.
15. Simpson AH. The blood supply of periosteum. J Anat 1985; 140:697—770. PMID: 4077705; PMCID: PMC1165093.
16. Augustin G, Antabak A, Davila S. The periosteum. Part 1: Anatomy, histology and molecular biology. Injury. 2007;38(10):1115-30. doi: 10.1016/j.

injury.2007.05.017
17. Zucman J. Studies on the vascular connections between periosteum, bone and muscle. Br J Surg 1960; 48:324—8. doi: 10.1002/bjs.18004820915.
18. Inman VT, & Saunders MJB. Referred Pain from Skeletal Structures. The Journal of Nervous and Mental Disease,1944; 99, 660–667. doi: 10.1097/00005053-194405000-00023
19. Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. Neuroscience. 2002;113(1):155-66. doi: 10.1016/s0306-4522(02)00165-3.
20. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al. Leptin regulates bone formation via the sympathetic nervous system. Cell. 2002;111(3):305-17. doi: 10.1016/s0092-8674(02)01049-8.
21. Elefteriou F. Neuronal signaling and the regulation of bone remodeling. Cell Mol Life Sci. 2005; 62:2339–49. doi: 10.1007/s00018-005-5175-3.
22. Mogi M, Kondo A, Kinpara K, Togari A. Anti-apoptotic action of nerve growth factor in mouse osteoblastic cell line. Life Sci. 2000;67(10):1197-206. doi: 10.1016/s0024-3205(00)00705-0.
23. Togari A, Mogi M, Arai M, Yamamoto S, Koshihara Y. Expression of mRNA for axon guidance molecules, such as semaphorin-III, netrins and neurotrophins, in human osteoblasts and osteoclasts. Brain Res. 2000; 878: 204–209. doi: 10.1016/s0006-8993(00)02700-1.
24. Yada M, Yamaguchi K, Tsuji T. NGF stimulates differentiation of osteoblastic MC3T3-E1 cells. Biochem Biophys Res Commun. 1994;205(2):1187-93. doi: 10.1006/bbrc.1994.2791.
25. Wang L, Zhou S, Liu B, Lei D, Zhao Y, Lu C, et al. Locally applied nerve growth factor enhances bone consolidation in a rabbit model of mandibular distraction osteogenesis. J Orthop Res. 2006;24(12):2238-45. doi: 10.1002/jor.20269.
26. Hayashi M, Nakashima T, Taniguchi M, Kodama T, Kumanogoh A, Takayanagi H. Osteoprotection by semaphorin 3A. Nature 2012; 485: 69–74. doi: 10.1038/nature11000.
27. Chang H, Knothe Tate ML. Concise review: the periosteum: tapping into a reservoir of clinically useful progenitor cells. Stem Cells Transl Med. 2012;1(6):480-91. doi: 10.5966/sctm.2011-0056.
28. Jaffee EM, Dranoff G, Cohen LK, Hauda KM, Clift S, Marshall FF, et al. High efficiency gene transfer into primary human tumor explants without cell selection. Cancer Res. 1993; 53:2221–6. PMID: 8485707.
29. Fan W, Crawford R, Xiao Y. Structural and cellular differences between metaphyseal and diaphyseal periosteum in different aged rats. Bone. 2008; 42:81–9. doi: 10.1016/j.bone.2007.08.048.
30. Uchiyama E, Yamakoshi K, Sasaki T. Measurement of mechanical characteristics of tibial periosteum and evaluation of local differences. J Biomech Eng. 1998; 120:85–91. doi: 10.1115/1.2834311.
31. Lin Z, Fateh A, Salem DM, Intini G. Periosteum: biology and applications in craniofacial bone regeneration. J Dent Res. 2014; 93:109–16. doi: 10.1177/0022034513506445
32. Uddstrumer L. The osteogenic capacity of tubular and membranous bone periosteum. A qualitative and quantitative experimental study in growing rabbits. Scand J Plast Reconstr Surg. 1978; 12:195–205. doi: 10.3109/02844317809012995.
33. Ogita M, Rached MT, Dworakowski E, Bilezikian JP, Kousteni S. Differentiation and proliferation of periosteal osteoblast progenitors are differentially regulated by estrogens and intermittent parathyroid hormone administration. Endocrinology.2008;149(11):5713–23. doi: 10.1210/en.2008-0369.
34. Turner RT, Bleiberg B, Colvard DS, Keeting PE, Evans G, Spelsberg TC. Failure of isolated rat tibial periosteal cells to 5 alpha reduce testosterone to 5 alpha-dihydrotestosterone. J Bone Miner Res. 1990; 5:775–9. doi: 10.1002/jbmr.5650050715.
35. Bikle D, Majumdar S, Laib A, Powell-Braxton L, Rosen C, Beamer W, Nau- man E, Leary C, Halloran B. The skeletal structure of insulin-like growth factor -Ideficient mice. J Bone Miner Res. 2001; 16:2320–9. doi: 10.1359/jbmr.2001.16.12.2320.
36. Rauch F. Bone growth in length and width: The Yin and Yang of bone stability. J Musculoskelet Neuronal Interact. 2005;5(3):194-201. PMID: 16172510.
37. Baron R. General principles of bone biology. In: Favus MJ (ed) Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 5th ed. American Society for Bone and Mineral Research, Washington DC; 2003:1-8. doi:10.1002/9781119266594.ch85.
38. Seeman E. Periosteal bone formation - a neglected determinant of bone strength. N Engl J Med 2003; 349:320-323. doi: 10.1056/NEJMp038101
39. Rackard SM, Carr AJ, Callanan JJ, Bellenger CR. An avian model of limb deviation induced by periosteal surgery. Res Vet Sci. 2002;73(3):237-41. doi: 10.1016/s0034-5288(02)00035-8.
40. Sansone JM, Wilsman NJ, Leiferman EM, Noonan KJ. The effect of periosteal resection on tibial growth velocity measured by micro transducer technology in lambs. J Pediatr Orthop. 2009; 29(1):61-7. doi: 10.1097/BPO.0b013e3181929c71.
41. Watanabe-Takano H, Ochi H, Chiba A, Matsuo A, Kanai Y, Fukuhara S, et al. Mechanical load regulates bone growth via periosteal Osteocrin. Cell Rep. 2021;36(2):109380. doi: 10.1016/j.celrep.2021.109380.
42. Kanai Y, Yasoda A, Mori KP, Watanabe-Takano H, Nagai-Okatani C, Yamashita Y, et al. Circulating osteocrin stimulates bone growth by limiting C-type natriuretic peptide clearance. J Clin Invest.

2017;127(11):4136-4147. doi: 10.1172/JCI94912.
43. Bertram JE, Polevoy Y, Cullinane DM. Mechanics of avian fibrous periosteum: tensile and adhesion properties during growth. Bone. 1998;22(6):669-75. doi: 10.1016/s8756-3282(98)00035-0.
44. Wilkins KE. Principles of fracture remodeling in children. Injury. 2005;36 Suppl 1: A3-11. doi: 10.1016/j.injury.2004.12.007.
45. Yiannakopoulos CK, Kanellopoulos AD, Trovas GP, Dontas IA, Lyritis GP. The biomechanical capacity of the periosteum in intact long bones. Arch Orthop Trauma Surg. 2008;128(1):117-20. doi: 10.1007/s00402-007-0433-5.
46. Hagino H, Okano T, Akhter MP, Enokida M, Teshima R. Effect of parathyroid hormone on cortical bone response to in vivo external loading of the rat tibia. J Bone Miner Metab. 2001;19(4):244-50. doi: 10.1007/s007740170027.
47. Rooney AM, Bostrom MPG, Dempster DW, Nieves JW, Zhou H, Cosman F. Loading modality and age influence teriparatide-induced bone formation in the human femoral neck. Bone. 2020; 136:115373. doi: 10.1016/j.bone.2020.115373.
48. Baker CE, Moore-Lotridge SN, Hysong AA, Posey SL, Robinette JP, Blum DM, et al. Bone Fracture Acute Phase Response-A Unifying Theory of Fracture Repair: Clinical and Scientific Implications. Clin Rev Bone Miner Metab. 2018;16(4):142-158. doi: 10.1007/s12018-018-9256-x.
49. Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, et al. The hypoxia-inducible factor alpha pathway couples' angiogenesis to osteogenesis during skeletal development. J Clin Invest. 2007;117(6):1616-26. doi: 10.1172/JCI31581.
50. Trueta J, Morgan JD. The vascular contribution to osteogenesis. I. Studies by the injection method. J Bone Joint Surg Br. 1960;42-B:97-109. doi: 10.1302/0301-620X.42B1.97.
51. Mahajan A. Periosteal pedicle graft for the treatment of gingival recession defects: a novel technique. Aust Dent J. 2009;54(3):250-4. doi: 10.1111/j.1834-7819.2009.01128.x.
52. Reynders P, Becker JH, Broos P. Osteogenic ability of free periosteal autografts in tibial fractures with severe soft tissue damage: an experimental study. J Orthop Trauma. 1999;13(2):121-8. doi: 10.1097/00005131-199902000-00009.
53. Barckman J, Baas J, Sшrensen M, Bechtold JE, Soballe K. Periosteal augmentation of allograft bone and its effect on implant fixation - an experimental study on 12 dogs(). Open Orthop J. 2013; 7:18-24. doi: 10.2174/1874325001307010018
54. Baldwin JG, Wagner F, Martine LC, Holzapfel BM, Theodoropoulos C, Bas O, et al. Periosteum tissue engineering in an orthotopic in vivo platform. Biomaterials. 2017; 121:193-204. Periosteum tissue engineering in an orthotopic in vivo platform. doi: 10.1016/j.biomaterials.2016.11.016.
55. Singh R, Chauhan V, Chauhan N, Sharma S. Transplantation of free tibial periosteal grafts for the repair of articular cartilage defect: An experimental study. Indian J Orthop. 2009;43(4):335-41. doi: 10.4103/0019-5413.55973.
56. McCarthy HS, Roberts S. A histological comparison of the repair tissue formed when using either Chondrogide (®) or periosteum during autologous chondrocyte implantation. Osteoarthritis Cartilage. 2013;21(12):2048-57. doi: 10.1016/j.joca.2013.10.004
57. Santić V, Cvek SZ, Sestan B, Bobinac D, Tudor A, Miletić D, Nemec B. Treatment of tibial bone defect with rotational vascular periosteal graft in rabbits. Coll Antropol. 2009;33(1):43-50. PMID: 19408602
58. Canalis RF, Burstein FD. Osteogenesis in vascularised periosteum. Interactions with underlying bone. Arch Otolaryngol. 1985;111(8):511-6. doi: 10.1001/archotol.1985.00800100059007.
59. Vugelin E, Jones NF, Lieberman JR, et al. Prefabrication of bone by use of a vascularised periosteal flap and bone morphogenetic protein. Plast Reconstr Surg 2002; 109:190—8. doi: 10.1097/00006534-200201000-00029.
60. Rubak JM. Osteochondrogenesis of free periosteal grafts in the rabbit iliac crest. Acta Orthop Scand 1983; 54:826-831. doi: 10.3109/17453678308992916.
61. Ranta R, Ylipaavalniemi P, Altonen M, Calonius PE. Transplantation of free tibial periosteal graft on alveolar bone defect in adult rabbit. Int J Oral Surg. 1981;10(2):122-7. doi: 10.1016/s0300-9785(81)80021-x
62. Ritsilä V, Alhopuro S. Spinal fusion with free periosteal grafts and its effect on vertebral growth in young rabbits. J Bone Joint Surg Br. 1975;57(4):500-5. PMID: 1194319.
63. Kayapinar R., Saridogan K., Kutlu A., Gurbuz H. The effects of free periosteal graft on fracture healing in rabbits. Acta Orthopaedica et Traumatologica Turcica. 2006; 26(2): 122-124. doi: 10.3944/aott.v26i2.1317
64. Liu JY, Wang D, Cheng HH. Experimental study of the osteogenic capacity of periosteal allografts: a preliminary report. Microsurgery. 1994;15(2):87-92. doi: 10.1002/micr.1920150202.
65. Hoffman MD, Benoit DS. Emerging ideas: Engineering the periosteum: revitalizing allografts by mimicking autograft healing. Clin Orthop Relat Res. 2013;471(3):721-6. doi: 10.1007/s11999-012-2695-7
66. Ueno T, Kagawa T, Fukunaga J, Mizukawa N, Sugahara T, Yamamoto T. Evaluation of osteogenic/chondrogenic cellular proliferation and differentiation in the xenogeneic periosteal graft. Ann Plast Surg. 2002;48(5):539-45. doi: 10.1097/00000637-200205000-00016.
67. Chen X, Yu B, Wang Z, Li Q, Dai C, Wei J. Progress of Periosteal Osteogenesis: The Prospect of in Vivo

Bioreactor. Orthop Surg. 2022;14(9):1930-1939. doi: 10.1111/os.13325.
68. Han D, Guan X, Wang J, Wei J, Li Q. Rabbit tibial periosteum and saphenous arteriovenous vascular bundle as an in vivo bioreactor to construct vascularised tissue-engineered bone: a feasibility study. Artif Organs. 2014;38(2):167-74. doi: 10.1111/aor.12124
69. Zhao J, Hu J, Wang S, Sun X, Xia L, Zhang X, et al. Combination of beta-TCP and BMP-2 gene-modified bMSCs to heal critical size mandibular defects in rats. Oral Dis. 2010;16(1):46-54. doi: 10.1111/j.1601-0825.2009.01602.x
70. Tatara AM, Koons GL, Watson E, Piepergerdes TC, Shah SR, Smith BT, et al. Biomaterials-aided mandibular reconstruction using in vivo bioreactors. Proc Natl Acad Sci U S A. 2019;116(14):6954-6963. doi: 10.1073/pnas.1819246116.
71. Soldado F, Fontecha CG, Barber I, Velez R, Llusa M, Collado D, et al. Vascularised fibular periosteal graft: a new technique to enhance bone union in children. J Pediatr Orthop. 2012; 32:308–313. doi: 10.1097/BPO.0b013e31824b2843.
72. Du MH, Ding Y, Shi X, Xu RJ. The Periosteal Autografts Transplantation for Cartilage Defects of the Hip in Older Children with Developmental Dysplasia as an Adjunctive Procedure. Medicine (Baltimore). 2016; 95(17): e3432. doi: 10.1097/MD.0000000000003432.
73. Soldado F, Barrera-Ochoa S, Bergua-Domingo JM, Domenech P, Corona PS, Knorr J. Bone nonunion management in children with a vascularised tibial periosteal graft. Microsurgery. 2020; 40(7):760-765. doi: 10.1002/micr.30655
74. Barrera-Ochoa S, Martin-Dominguez LA, Campillo-Recio D, Alabau-Rodriguez S, Mir-Bullo X, Soldado F. Are Vascularised Periosteal Flaps Useful for the Treatment of Difficult Scaphoid Nonunion in Adults? A Prospective Cohort Study of 32 Patients. J Hand Surg Am. 2020; 45(10):924-936. doi: 10.1016/j.jhsa.2020.06.013
75. Christen T, Krähenbühl SM, Müller CT, Durand S. Periosteal medial femoral condyle free flap for metacarpal nonunion. Microsurgery. 2022;42(3):226-230. doi: 10.1002/micr.30826
76. Soldado F, Barrera-Ochoa S, Romero-Larrauri P, Nguyen TQ, Diaz-Gallardo P, Guerra E, et al. Congenital pseudarthrosis of the tibia: Rate of and time to bone union following contralateral vascularised periosteal tibial graft transplantation. Microsurgery. 2022;42(4):326-332. doi: 10.1002/micr.30868
77. Liu Y, Yang G, Zhu G, Tan Q, Wu J, Liu K, Tang J, Mei H. Application of the "telescopic rod" in a combined surgical technique for the treatment of congenital pseudarthrosis of the tibia in children. J Orthop Surg Res. 2021;16(1):532. doi: 10.1186/s13018-021-02649-2.
78. Abrahamsson P, Isaksson S, Gordh M, Andersson G. Periosteal expansion of rabbit mandible with an osmotic self-inflatable expander. Scand J Plast Reconstr Surg Hand Surg. 2009;43(3):121-5. doi: 10.1080/02844310902771798.
79. Abrahamsson P, Isaksson S, Gordh M, Andersson G. Onlay bone grafting of the mandible after periosteal expansion with an osmotic tissue expander: an experimental study in rabbits. Clin Oral Implants Res. 2010;21(12):1404-10. doi: 10.1111/j.1600-0501.2010.01967.x.
80. Abrahamsson P, WΔlivaara DE, Isaksson S, Andersson G. Periosteal expansion before local bone reconstruction using a new technique for measuring soft tissue profile stability: a clinical study. J Oral Maxillofac Surg. 2012;70(10): e521-30. doi: 10.1016/j.joms.2012.06.003.
81. Radovan C. Tissue expansion in soft-tissue reconstruction. Plast Reconstr Surg. 1984;74(4):482-92. doi: 10.1097/00006534-198410000-00005
82. Abrahamsson P, Isaksson S, Andersson G. Guided bone generation in a rabbit mandible model after periosteal expansion with an osmotic tissue expander. Clin Oral Implants Res. 2011;22(11):1282-8. doi: 10.1111/j.1600-0501.2010.02108.x.
83. Manders EK, Schenden MJ, Furrey JA, Hetzler PT, Davis TS, Graham WP 3rd. Soft-tissue expansion: concepts and complications. Plast Reconstr Surg. 1984;74(4):493-507. doi: 10.1097/00006534-198410000-00007.
84. Cunha MS, Nakamoto HA, Herson MR, Faes JC, Gemperli R, Ferreira MC. Tissue expander complications in plastic surgery: A 10-year experience. Rev Hosp Clin Fac Med Sro Paulo. 2002;57(3):93-7. doi: 10.1590/s0041-87812002000300002.
85. Asa'ad F, Rasperini G, Pagni G, Rios HF, Giannì AB. Pre-augmentation soft tissue expansion: an overview. Clin Oral Implants Res 2016; 27:505-22. doi: 10.1111/clr.12617.
86. Johnson TM, Lowe L, Brown MD, Sullivan MJ, Nelson BR. Histology and physiology of tissue expansion. J Dermatol Surg Oncol 1993; 19:1074-8. doi: 10.1111/j.1524-4725.1993.tb01002.x.
87. Uijlenbroek, H.J.J.; Liu, Y.; Wismeijer, D. Soft Tissue Expansion: Principles and Inferred Intraoral Hydrogel Tissue Expanders. Dent. Oral Craniofac. Res. 2016, 1, 178–185. doi: 10.15761/DOCR.1000140
88. Delloye C, Cornu O, Druez V, Barbier O. Bone allografts: What they can offer and what they cannot. J Bone Joint Surg Br. 2007;89(5):574-9. doi: 10.1302/0301-620X.89B5.19039.
89. Karaoglu S, Baktir A, Kabak S, Arasi H. Experimental repair of segmental bone defects in rabbits by demineralized allograft covered by free autogenous periosteum. Injury. 2002 Oct;33(8):679-83. doi: 10.1016/s0020-1383(02)00086-4.
90. Zhang D, Huang D, Huang Y, Liu Y, Lin B, Yu

C, Mou Y, Wu W, Zhang H, Lin H. Efficacy of combined therapy of periosteum and bone allograft in a critical-sized defect model in New Zealand white rabbits. Med Sci Monit. 2014; 20:2394-403. doi: 10.12659/MSM.891103.
91. Soldado F, Barrera-Ochoa S, Fontecha CG, Haddad S, Barastegui D, Barber I, et al. Vascularised periosteal graft from the first meta- tarsal bone: A new technique to prevent collapse of osteonecrosis of the talus in children. A case report. Microsurgery 2013; 33:56–59. doi: 10.1002/micr.22045.
92. Zhang W, Wang N, Yang M, Sun T, Zhang J, Zhao Y, Huo N, Li Z. Periosteum and development of the tissue-engineered periosteum for guided bone regeneration. J Orthop Translat. 2022; 33:41-54. doi: 10.1016/j.jot.2022.01.002.
93. Fan W, Crawford R, Xiao Y. Enhancing in vivo vascularised bone formation by cobalt chloride-treated bone marrow stromal cells in a tissue engineered periosteum model. Biomaterials 2010;31: 3580–3589. doi: 10.1016/j.biomaterials.2010.01.083.
94. Nakahara H, Bruder SP, Goldberg VM, Caplan AI. In vivo osteochondrogenic potential of cultured cells derived from the periosteum. Clin Orthop Relat Res. 1990;(259):223-32. PMID: 2208860.
95. Arnsdorf EJ, Jones LM, Carter DR, Jacobs CR. The periosteum as a cellular source for functional tissue engineering. Tissue Eng Part A. 2009;15(9):2637-42. doi: 10.1089/ten.TEA.2008.0244.
96. Ferretti C. Periosteum derived stem cells for regenerative medicine proposals: Boosting current knowledge. World J Stem Cells. 2014;6(3):266-77. doi: 10.4252/wjsc.v6.i3.266
97. Schunmeyr B, Clavin N, Avraham T, Longo V, Mehrara BJ. Synthesis of a tissue-engineered periosteum with acellular dermal matrix and cultured mesenchymal stem cells. Tissue Eng Part A. 2009;15(7):1833-41. doi: 10.1089/ten.tea.2008.0446.
98. Hassibi H, Farsinejad A, Dabiri S, Voosough D, Mortezaeizadeh A, Kheirandish R, et al. Allogenic Bone Graft Enriched by Periosteal Stem Cell and Growth Factors for Osteogenesis in Critical Size Bone Defect in Rabbit Model: Histopathological and Radiological Evaluation. Iran J Pathol. 2020 Summer;15(3):205-216. doi: 10.30699/ijp.2020.101715.2013.
99. Hattori K, Yoshikawa T, Takakura Y, Aoki H, Sonobe M, Tomita N. Bio-artificial periosteum for severe open fracture--an experimental study of osteogenic cell/collagen sponge composite as a bio-artificial periosteum. Biomed Mater Eng. 2005;15(3):127-36. PMID: 15911994.
100. Ma D, Yao H, Tian W, Chen F, Liu Y, Mao T, Ren L. Enhancing bone formation by transplantation of a scaffold-free tissue-engineered periosteum in a rabbit model. Clin. Oral Impl. Res. 22, 2011; 1193–1199. doi: 10.1111/j.1600-0501.2010.02091.x.
101. Martin I, Miot S, Barbero A, Jakob M, Wendt D. Osteochondral tissue engineering. J Biomech. 2007;40(4):750-65. doi: 10.1016/j.jbiomech.2006.03.008.
102. Sung MS, Jeong CH, Lim YS, Yoo WJ, Chung SK, Jung NY. Periosteal autograft for articular cartilage defects in dogs: MR imaging and ultrasonography of the repair process. Acta Radiol. 2011;52(2):181-90. doi: 10.1258/ar.2010.100087.
103. Hsiao HY, Cheng CM, Kao SW, Liu JW, Chang CS, Harhaus L, Huang JJ. The effect of bone inhibitors on periosteum-guided cartilage regeneration. Sci Rep. 2020;10(8372). doi: 10.1038/s41598-020-65448-5.
104. Redman SN, Oldfield SF, Archer CW. Current strategies for articular cartilage repair. Eur Cell Mater. 2005; 9:23-32. doi: 10.22203/ecm.v009a04.
105. Mackie EJ, Ahmed YA, Tatarczuch L, Chen KS, Mirams M. Endochondral ossification: how cartilage is converted into bone in the developing skeleton. Int J Biochem Cell Biol. 2008;40(1):46-62. doi: 10.1016/j.biocel.2007.06.009.
106. Moore SR, Heu C, Yu NY, Whan RM, Knothe UR, Milz S, et al. Translating Periosteum's Regenerative Power: Insights from Quantitative Analysis of Tissue Genesis with a Periosteum Substitute Implant. Stem Cells Transl Med. 2016;5(12):1739-1749. doi: 10.5966/sctm.2016-0004.
107. O'Driscoll SW. Technical considerations in periosteal grafting for osteochondral injuries. Clin Sports Med. 2001;20(2):379-402. doi: 10.1016/s0278-5919(05)70312-4.
108. O'Driscoll SW, Keeley FW, Salter RB. The chondrogenic potential of free autogenous periosteal grafts for biological resurfacing of major full-thickness defects in joint surfaces under the influence of continuous passive motion. An experimental investigation in the rabbit. J Bone Joint Surg Am. 1986;68(7):1017-35. PMID: 3745239
109. Jaroma HJ, Ritsilä VA. Reconstruction of patellar cartilage defects with free periosteal grafts. An experimental study. Scand J Plast Reconstr Surg Hand Surg. 1987;21(2):175-81. doi: 10.3109/02844318709078097.
110. Skoog T, Johansson SH. The formation of articular cartilage from free perichondrial grafts. Plast Reconstr Surg. 1976;57(1):1-6. doi: 10.1097/00006534-197601000-00001.
111. Bouwmeester SJ, Beckers JM, Kuijer R, van der Linden AJ, Bulstra SK. Long-term results of rib perichondrial grafts for repair of cartilage defects in the human knee. Int Orthop. 1997;21(5):313-7. doi: 10.1007/s002640050175.
112. Yoo H, Yoon T, Bae HS, Kang MS, Kim BJ. Does periosteum promote chondrogenesis? A comparison of free periosteal and perichondrial grafts in the regeneration of ear cartilage. Arch Craniofac Surg. 2021;22(5):260-267. doi: 10.7181/

acfs.2021.00423
113. Yang Y, Topol L, Lee H, Wu J. Wnt5a and Wnt5b exhibit distinct activities in coordinating chondrocyte proliferation and differentiation. Development. 2003;130(5):1003-15. doi: 10.1242/dev.00324.
114. Ito Y, Fitzsimmons JS, Sanyal A, Mello MA, Mukherjee N, O'Driscoll SW. Localization of chondrocyte precursors in periosteum. Osteoarthritis Cartilage. 2001;9(3):215-23. doi: 10.1053/joca.2000.0378.