The effect of bisphosphonate and platelet-rich plasma in anterior cruciate ligament reconstruction: an article review

Tangkas Sibarani1,2*, Bambang Purwanto2, Ambar Mudigdo1,3, Brian Wasita1,3

ABSTRACT

ACL rupture is a common injury often resulting from previously healthy individuals’ non-contact knee injuries. ACL rupture in young adults and teenagers is becoming more common, contrary to earlier theories that suggested ACL damage was uncommon in skeletally immature people. This risk is significantly raised by concomitant meniscal injury whether or not an ACL reconstruction is undertaken. Although surgical management with allograft or autograft reconstruction can be achieved successfully, there are some serious complications following ACL reconstruction. The supply of autografts is limited, especially in situations with numerous ligament injuries or re-ruptures, which might result in morbidity at the donor site. Allografts can increase the spread of illness and trigger an inflammatory response, which is a drawback. There has been much interest in a tissue-engineered ACL graft because of these issues and current developments in bioengineering and regenerative medicine.

INTRODUCTION

ACL rupture is a common injury often resulting from previously healthy individuals’ non-contact knee injuries. According to current findings, ACL rupture in young adults and teenagers is becoming more common, contrary to earlier theories that suggested ACL damage was uncommon in skeletally immature people. The inability to engage in athletics, reconstructive surgery, and protracted recovery are some short-term effects of ACL rupture. In the long run, practically everyone who tears an ACL is at elevated risk of osteoarthritis and disability. This risk is significantly raised by concomitant meniscal injury whether or not an ACL reconstruction is undertaken.3 There are 200,000 Anterior Cruciate Ligament (ACL) injuries annually in the united states, with 60,000 to 150,000 cases treated with ACL reconstruction. The current gold standard for treating ACL injury is ACL repair.3 Another research reported that the patients joint in the ACL community of Indonesia mostly was men 89.3%, with an average age of 27.5±6.6 years old.4

The outcomes of this treatment are mainly defined by the two biological processes: graft to bone healing and ligamentization of the tendon graft.5 Both autograft and allograft repair are quite successful, according to a meta-analysis. Recent research indicates that the failure rates of autografts and allografts (about 6% and 7%, respectively) are not significantly different. Autografts are the first option in cost-effectiveness analysis since the price difference is the primary consideration. However, there will be circumstances where an allograft may be desired or the only practical choice, particularly in revision ACL surgery.6 Although surgical management with allograft or autograft reconstruction can be achieved successfully, there are some serious complications following ACL reconstruction.7

The supply of autografts is limited, especially in situations with numerous ligament injuries or re-ruptures, which might result in morbidity at the donor site. Allografts can increase the spread of illness and trigger an inflammatory response, which is a drawback. The use of a tissue-engineered ACL graft has attracted much interest because of these issues and current developments in bioengineering and regenerative medicine.7 According to recent research, following an ACL repair, the bone marrow density surrounding the knee area diminishes. Platelet Rich Plasma (PRP) and Bisphosphonate are the substrates that could ameliorate this phenomenon. Therefore, this review aims to compile evidence of PRP and bisphosphonate and its effect on the tendon-bone interface in ACL reconstruction.

Keywords: Biphosphonate, PRP, ACL, ACL reconstruction, Bone-tendon interface.

have advanced, an understanding of the biological process of tendon graft healing should be acquired. Based on MRI, there are 3 steps of graft healing in ACL graft: early healing, proliferation, and the maturation phase. ACL graft recovery is monitored with a CT scan to track changes in the bone tunnel. Synovialization and vascularization are observed using direct arthroscopy.

The healing process starts by changing the substance within the graft during the first 6 months. It was shown in the increase of magnetic resonance graft signal indicates graft oedema allowing surgical implantation, there is an accumulation of inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and transforming growth factor-beta (TGF-b). The graft develops avascular necrosis concurrently, primarily in the center. The emergence of the inflammation process attracts the immune system and mesenchymal stromal cells (MSCs) to the injury site. These MSCs will replace the necrosis tissue. MSC will proliferate and differentiate. In addition, both MCS and inflammatory factors will activate the angiogenic factors. Thus, revascularization will happen.

The proliferation phase consists of two processes—the revascularization and popularisation of the necrotic cell of the tendon graft. The revascularization will define the subsequent progress of cell popularisation. The previous inflammatory reaction induces Vascular Endothelial Growth Factor (VEGF) production, thus forming vascular ingrowth in the autograft as early as 3 weeks. From there on, the fibroblast originated from the synovial membrane, and the residual stump of ACL and osteoblast from bone marrow stem cells repopularised the vacant connective tissue matrix of the autograft and the bone tunnel. The tendon graft-to-bone tunnel created by Sharpey’s fibers is incorporated by remodeling enzymes produced during the proliferation phase, which is also linked to better biomechanical healing complex features. The bone tunnel’s recovery, however, varies depending on the area.

Endochondral ossification is analogous to the maturation stage. The bone tunnel environment’s wall resembles the fracture site. The primary bone remodeling factors that result in osseous integration are bone morphogenetic proteins (BMP), particularly BMP-2 and BMP-72. When the tissue at the tendon-bone junction begins to mineralize, tendon-bone healing occurs. After the transplant has been incorporated into the nearby bone, the bone develops into the tendon’s outer layer. The tendon matures until its matrix comprises orientated collagen fibers, and the fibrous interface is no longer visible.

Platelet Rich Plasma (PRP)

PRP has a suitable substance to promote the healing process for bone and tendon damage. The association between the use of PRP and the repair of ACL has been the subject of several investigations. Concerning the usage of PRP in ACL repair, we will present helpful information in this review for a better understanding and growth.

Platelet Rich Plasma comprises orientated collagen fibers, and the fibrous interface is no longer visible. A component of plasma called PRP is made up mostly of platelets from autologous blood. Transforming growth factor (TGF)-b1, platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like growth factor (IGF)-1 are among the growth factors and mediators found in platelets’ alpha granules that promote cell healing. The PRP advancements can also be used as a therapeutic alternative to speed up and stimulate soft tissue repair and regeneration. Growth factors and proteins like fibrinogen are abundant in PRP. The growth factors are crucial for controlling growth and developing many different tissues. They quicken wound healing and tissue regeneration by enhancing cellular proliferation, matrix creation, osteoid development, connective tissue repair, angiogenesis, and collagen synthesis.

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Description</th>
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<tr>
<td>BMP</td>
<td>促进骨自组织再生，是骨生长因子中的主要成分。</td>
</tr>
<tr>
<td>PRP</td>
<td>提高软组织的愈合速度和质量。</td>
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Figure 1. The graft healing process in ACL.
release bioactive chemicals, cell migration (delivery of serum-derived cytokines), and metabolism in pathologic conditions.\textsuperscript{12,17-19} PRP has several benefits and may be employed in surgical operations because of its composition. This is because it has a certain growth factor that may promote cell migration, proliferation, and differentiation. By interacting with leukocytes and secreting cytokines, chemokines, and other inflammatory mediators at the site of action, platelets swiftly distribute to damaged areas, disintegrate fast, and may even influence inflammatory processes. One of the many growth factors that control cell proliferation, migration, and division is PDGF, which is released by platelets.\textsuperscript{20}

PRP promoted the development of fibrocartilage, and following ACL repair, the replacement ACL resembled the genuine ACL more closely. PRP could facilitate osseointegration in the tendon-to-bone tunnel and boost the mechanical capabilities of ACL transplants. PRP may promote the growth of osteoblasts, bone marrow stem cells (BMSC), and the mRNA expression of genes (ALP, OCN, and RUNX2) linked to tendon-to-bone repair. Additionally, it enhanced early revascularization at the interface zone between the graft and the tibial bone tunnel at the tendon-bone junction in an ACL reconstruction mode which aided in the early healing phase. After 12 weeks, BMSCs and PRP were predicted to improve graft maturation. However, MRIs afterward revealed that PRP therapy greatly improved allograft graft maturation and cortical bone formation.\textsuperscript{13,21} Regarding the impact of PRP on the maturation of ACL grafts, several studies have shown that this treatment can accelerate this process by up to 50%.\textsuperscript{22} Transplant-bone tunnel integration is the second element of successful biologic healing of an ACL transplant. Another study conducted a controlled, double-blind evaluation of the efficacy of PRP gel therapy for hamstring autograft ACL restoration. The researchers observed that utilizing PRP after three months, MRI showed enhanced vascularity at the ACL graft-bone contact.\textsuperscript{22}

### Bisphophonate

The primary drugs used to treat osteoclast-mediated bone loss brought on by osteoporosis, Paget’s disease of the bones, malignancies that have metastasized to the bones, multiple myeloma, and hypercalcemia of malignancy are bisphosphonates. In addition to their officially recognized uses, bisphosphonates are frequently used to prevent and treat various other skeletal problems, such as low bone mass and osteogenesis imperfecta.\textsuperscript{23} Bisphosphonates are now often utilized in ACL repair surgery to speed up tendon recovery. Numerous publications have documented effects on the bone tunnel.\textsuperscript{24}

The enthesis is a transitional fibrocartilage tissue covering the area where tendons and ligaments join bones. The ligament, unmineralized fibrocartilage, mineralized fibrocartilage, and bone are typically the four different sections that make up this location. This place doesn’t undergo regeneration during ACL reconstruction. This site normally heals by fibrovascular site rather than the normal reformation of the insertion site.\textsuperscript{25,26}

Clinical study has shown evidence of a transient, local, and reversible decrease in Bone Marrow Density (BMD) and peri-tunnel bone loss during ACL reconstruction. This could affect the clinical outcomes of ACL reconstruction, as bone tunnel loss negatively correlates to the tendon-bone interface strength due to graft osteointegration disturbance. The decrease in BMD could cause undermine the graft-bone tunnel complex and bone fracture. This phenomenon could be brought on by enhanced osteoclastic activity by generating cytokines linked to bone resorption.\textsuperscript{24,25} Lui et al. reported a histologically improved tendon graft-to-bone tunnel integration and tunnel graft integrity after alendronate treatment compared to saline injection. A comparison of the tendon-bone interface in the group given alendronate also found high integrity and smaller tunnel diameter than the control group.\textsuperscript{24}

Bisphosphonate’s role in bone-tendon interface healing after ACL restoration has yet to be studied in clinical studies. The findings of four experiments on the subject are nevertheless included in our review. Rats were the intervention subjects in each study that made up this review. The ipsilateral flexor digitorum longus tendon was employed in three experiments with the identical ACL restoration technique. The extracted characteristics of included studies can be seen in Table 1.

### Bisphosphonate and PRP for Bone Tunnel Healing

According to Hjorthaug et al., the bisphosphonate zoledronic acid (ZA) substantially reduced pullout strength compared to control by 19% (p = 0.009) at 3 and 6 weeks for tendon-to-bone repair. Additionally, stiffness was statistically decreased by 43% by the bisphosphonate (p = 0.004). However, neither Bone Mineral Density (p=0.2) nor Bone Mineral Content (p=0.9) were impacted by ZA administration. Unfavorable findings showed that a single dose of ZA decreased pullout strength and stiffness of the tendon-bone interface without showing any signs of localized bone loss and without a change in BMD during the intervention group and the control group.\textsuperscript{25}

However, Hjorthaug et al. findings tended to conflict with other papers already in the public domain. While alendronate injection was shown by Lui et al. to lessen peri-tunnel bone loss as evaluated by CT-scan,\textsuperscript{24} Thomopoulos et al. showed that alendronate could prevent regional bone loss and enhance tendon-to-bone repair.\textsuperscript{27} Clodronate, a bisphosphonate that specifically promotes macrophage death to speed healing, as seen by improved collagen fiber continuity and a larger degree of tendon-bone contact remodeling, was also reported by Hays et al.\textsuperscript{26}

Alendronate was demonstrated to reduce peritunnel bone loss during repair significantly. Week 6 dramatically enhanced intra-tunnel graft integrity, graft-bone tunnel integration, and peri-tunnel bone mass and density along all tunnel areas. Alendronate was shown to increase mineralized tissue inside the bone tunneling repair. Week 6 dramatically enhanced intra-tunnel graft integrity, graft-bone tunnel integration, and peri-tunnel bone mass and density along all
Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Animal</th>
<th>Samples</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Hjorthaug et al., 2018⁴⁸ | Wistar Rats   | 92      | Bone tunneling of Achilles tendon + single dose Zoledronic Acid (0.1 mg/kg IV) versus control group | 1. Pull-out strength  
2. Stiffness  
3. Energy absorption  
4. Elongation  
5. Differences in BMD and BMC |
| Hays et al., 2008⁶⁶ | Male Sprague-Dawley Rats | 192 | The ipsilateral flexor digitorum longus tendon repair of the right knee combined with a single Clodronate injection as compared to the control group | 1. Histomorphometry  
2. Macrophage activity |
| Lui et al., 2012⁹⁹ | Male Sprague-Dawley Rats | 84 | ACL reconstruction combined with ipsilateral flexor digitorum longus tendon and subcutaneous Alendronate injections at varying doses | 1. Bone mass and mineralization density  
2. Biomechanical  
3. Histology  
4. Immunohistochemistry |
| Lui et al., 2013⁴⁴ | Male Sprague-Dawley Rats | 72 | ACL reconstruction with the ipsilateral flexor digitorum longus tendon and different alendronate dosages administered locally to the bone tunnel | 1. Bone mass and mineralization density  
2. Biomechanical  
3. Histology  
4. Graft bone tunnel integration  
5. Changes in peri-tunnel bone integration  
6. Bony changes in the contralateral knee |

Several studies show PDGF’s ability to promote bone growth, notably in periodontology. It has been demonstrated that these substances increase murine osteoblasts’ activity and proliferation while dramatically increasing the amount of vascularization in the osteoligamentous interface in vitro. On the other hand, PRP application enhanced anterior knee stability due to PDGF, according to research by Agir et al. (2017) and Rupreht et al. (2013).¹⁶,²² Conversely, Azcárate (2014) stated that using double spinning and leukocyte PRP systems in ACL surgery did not seem beneficial.¹⁵

CONCLUSION

Various contents of PRP and bisphosphonate have been proven to enhance tissue repair processes involving its cytokines and growth factors. Several results on the beneficial use of PRP and bisphosphonate after ACL construction still need to be clarified. Also, several studies stated that the use of this substance in those procedures remains to be seen. Further research must be held for the definite benefit of PRP and bisphosphonate on clinical application.

DISCLOSURE

Conflicts of Interest
The authors affirm that they do not have any competing interests.

Funding Sources
No particular grant was given to this research by any funding organization in the public, private, or nonprofit sectors.

Ethical Approval
This review does not require any form of ethical approval.

Authors contributions
The study was planned and prepared by TS and AM, who also carried out the research, reference gathering, and organization. BW and BP create a basic overview of all references. TS wrote the article’s first and last drafts. The content and similarity index of the paper is the responsibility of all authors, who also gave the final text a critical assessment and approval.

ACKNOWLEDGMENTS

The authors would like to thank the Doctorate Program of Medical Sciences, Faculty of Medicine, Universitas Sebelas Maret; Department of Orthopaedic and Traumatology, Faculty of Medicine, Universitas Sebelas Maret, and all the people who contributed to this research.

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