Clinical and Experimental Health Sciences

The Role of Biological Therapies in Orthopaedic Surgery: Investigating the Use of Stem Cells, Platelet-Rich Plasma (PRP), and Growth Factors to Enhance Bone Healing and Cartilage Regeneration in Musculoskeletal Injuries

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Abstract

Background: Bone and joint diseases of different etiology cause pain and can lead to fractures, arthrosis, and other illnesses, which significantly reducing patients' quality of life. Standard approaches for the management of damaged tissues include the surgical intervention and physiotherapy which however give moderate results from the point of view of functional recovery. Biological therapy is the method that is gradually gaining its popularity in the treatment of bone injuries and cartilage degradations through stem cells, PRP, and growth factors therapies at cellular level.

Aim: This work is planned as a systematic literature review and meta-analysis to assess the state of knowledge about applied stem cells, PRP, and growth factors in orthopaedic surgery and to identify how these treatments are incorporated into treatment algorithms for MSK injuries.

Method: A comprehensive clinical trial, observational, and case reports analysing stem cells, PRP, and growth factors' orthopaedic application have been implemented. The criteria for inclusion were articles including human participants and outcomes for bone healing and cartilage regeneration.

Results: Stem cell therapies especially MSCs evidenced an enhanced healing efficacy in cases of fracture and cartilage defects. PRP was helpful in increasing tissue healing rate, decreasing pain, and improving outcomes in ailments like osteoarthritis and tendon rupture. BMPs are the specific growth factors that have been used to enhance bone union and for cartilage repair. Hypersensitization of these agents in combination therapies enhanced healing outcomes when used in combination with other drugs. However, protocol hypertension and patient-related factors raised concerns about these treatments' standardisation.

Conclusion: Stem cells, PRP and growth factors belong to biological therapies demonstrated notable possibility to reconstruct tissue damages in musculoskeletal injuries. Future large sample clinical trials and long-term studies are required to achieve the optimal therapeutic effects and formulate the set of guidelines for clinical use for large groups of patients with the disease.

Keywords: stem cells, Platelet-Rich Plasma (PRP), growth factors, orthopedic surgery, bone healing, cartilage regeneration, biological therapies, musculoskeletal injuries.

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Introduction

The musculoskeletal injuries constitute one of the most dominant health risks in the global society with millions of people experiencing the injury annually. These include injuries to the bone, muscles, ligaments, tendons and cartilage which bring about alteration on the quality of a patients life. Thus, the injuries within the musculoskeletal system we are talking about can vary ranging from distal sprain and strains to proximal falls, fractures or such chronic diseases as osteoarthritis. These injuries again are not only the physical one but have severe impact on the mental wellbeing of the person may get secluded or lose their jobs. The increase in life expectancy of the population, the growing involvement in activities that require increased loading on the musculoskeletal system, such as high-intensity sports, etc., has led to the increased frequency of musculoskeletal injuries [1].

In general, conventional approaches of treating conditions in the field of orthopaedic surgery involve surgery, mechanical stabilization augmented by means of plates, screws, or pins, and physiotherapy in order to gain or regain function. Although these kinds of approaches are suitable for different kinds of injuries, they sometimes have disadvantages. For example, surgeries are likely to cause a lot of harm; they may be intricate, and patients may take a long time to recover. Moreover, specific situations indicate that the effectiveness of the healing process may not always be optimal, and it may take longer time or not succeed at all, primarily, in elderly or in people with chronic illnesses. Failure of a bone to heal or union that takes longer than usual and poor or delayed cartilage repair may lead to chronic pain and dysfunction. The increased number of orthopaedic surgeries also has an impact on health care delivery systems; researchers and clinicians are consequently forced to look for ways to improve the healing of the injured tissues and speed up their recovery in order to reduce the cost implication of such surgical procedures [2]. Organic treatments have taken the centre stage in the recent past as people turn to seek biological solutions in supplementing treatment of musculoskeletal injuries. The presumptions of these therapies are based on the possibility to stimulate the healing processes of the organism and improve the activity of tissue repair mechanisms. In this regard, biological therapies like stem cells, PRP, and growth factors are the potential candidate to be an option or potential supplement to the conventional therapy as they compose the therapeutic agents which are involved in the tissue repair and regeneration at the receptor molecular level. These therapies are not only focused on the reduction of healing times, but also on the enhancement of the quality of the regenerated tissue in situations that the body's ability to regenerate itself is not sufficient, such as in difficult injuries or in degenerative diseases.

Biological therapies can easily be described as perhaps the most significant idea ever to grace the sector of regenerative medicine especially for cases of orthopaedic surgery. These therapies employ chemicals that occur naturally and possess the ability to promote supporting tissues' cell growth and differentiation as well as form new tissues. The best known agents are stem cells, PRP and growth factors, all of which act in different ways to stimulate the healing process [3].

Recently, stem cells mainly mesenchymal stem cells (MSCs) have been paid much attention due to multipotent differentiation in vitro and in vivo such as bone, cartilage, muscle cells and so on. Many stem cells exist some of the most common stem cells include the bone marrow stem cells, stem cells found in adipose tissue and some are derived from umbilical cord blood. These cells not only facilitate the generation of new bone or cartilage but also help control inflammation that is characteristic of early healing episodes as soon as it is injected in the site of the injury. Their ability to differentiate and self renew makes stem cells ideal for use in difficult fractures, osteoarthritis and other degenerative joint diseases [4].

Platelet-rich plasma (PRP), in contrast, can be produced from the patient's blood and they are safe. PRP is therefore prepared from a blood sample by spinning it in a centrifuge thereby

enriching platelet dense area which contain such growth factors as Platelet- derived growth factor (PDGF), Vascular Endothelial Growth Factor (VEGF) and Transforming Growth factor-beta (TGF-β). These growth factors are essential in kick start and sustaining tissue repairing by fostering cell migration, stem cell division and formation of new blood vessels. Local applicant of PRP has beneficial effects on soft tissues reparative processes in the skin, tendons, ligaments and menisci and has been described to be useful in treatment of tendinopathies, muscle strains and osteoarthritis.

The third category of biological therapy is growth factors which are proteins produced by the human body and are considered being primary to the repair and remodelling process. In orthopaedic surgery commonly used growth factors are the bone morphogenetic proteins (BMPs) and insulin-like growth factor-1 (IGF-1) for the induction of bone and cartilage formation. For example, BMPs have been used in spinal fusions and non-union fractures to stimulate bone healing by stimulating the differentiation of mesenchymal cells into osteoblasts, the bone forming cells. An ideal method of delivering the growth factors is through direct injectable or via matrix in the tissue engineering in order to Favor good results [5].

The aim of this systematic review article is to outline and discuss the present state of knowledge about the effectiveness of biological treatments for orthopaedic surgery: stem cells, PRP, and growth factors. These therapies have carried out well in preclinical as well as clinical trials, while their broad usage has been just modest due to inconsistency in treatment protocols and variations in the results of several studies. Therefore, the purpose of this article is to synthesize literature data on the incorporation of these therapies into therapeutic regimens for bone and cartilage regeneration.

The second purpose is to explore how these therapies can be best used in clinical practice. This involves identification of stem cell's best sources and preparation and assessment of optimal dose and delivery method of growth factors together with PRP. Moreover, personal characteristics of the patient—age and other diseases, and the type of the injury—should also be considered when discussing biological treatments. Knowledge over these factors will assist clinicians fine- tune therapies to individual patients – and so achieve better outcomes with lower risk of adverse events [6].

Finally, this article endeavours to explore some of the issues and constraints that accompany biological therapies with respect to Osseous surgical procedures. However, main concerns that still remain include early results may not fully translate to a longer term, some of these treatments are expensive, side effects are of concern and long term follow up results are missing. Furthermore, compliance with the regulation and some ethical issues as related to stem cell usage have to be also taken into consideration with the as these therapies progress from experimental to routine use.

Therefore, it becomes apparent that the biological category is one of the most viable directions in the further development of orthopaedic surgery. However, more investigation has to be done to elaborate on these possibilities and to create uniform therapeutic approaches. It is the hope of the authors of this article that by exploring the potential of stem cells, PRP, and growth factors in musculoskeletal injury repair the academic community will gain a greater understanding of potential interventions that are capable of positively and significantly impacting patient outcome in the field of regenerative medicine [7].

Material and Methods

This study uses the systematic review approach in the integration of available literature on the application of biological therapies, including stem cells, PRP and growth factors in orthopaedic surgery. The main aim is to draw conclusions about the efficiency of these therapies in promotion of rarefactive bone healing and chondrogenesis. Systematic reviews occur in biomedical research because they enable the synthesis and critique of all obtainable research data on sensible research

hypotheses, which forms the foundation of contemporary clinical practice.

In this review, clinical trials, observational studies and case reports targeting the use of biological tissues in the management of musculoskeletal injuries were captured. The study involved criteria of inclusion and exclusion as we selected and eliminated variables to include in the study. To be included in the review, studies had to meet the following inclusion criteria: The trials had to enrol patients with MRIs featuring musculoskeletal injuries; the intervention had to include at least one biological treatment modify including stem cells, PRP or growth factors; and the results had to be reported in terms of bone/tissue heal, cartilage regeneration or patients' self reported pain or function. Excluded were cad publications excluding animal model, if the intervention was not clearly described or if the outcome measurements were inadequate for assessment. Secondly, this review excluded sources in non English language and peer reviewed articles published before 15 years ago to capture up-to-date data [8]. The following are the biological therapies reviewed in this paper; Stem cells, PRP and growth factors. These agents have become more employed in orthopaedic surgery because of the ability to regenerate tissue at the cellular level. Every therapy was found to have a unique role in musculoskeletal tissue repair and the therapy was researched for its usability in bone regeneration and chondrogenic differentiation.

In orthopaedics, cells with differentiation potential like mesenchymal stem cells (MSCs) have enormous potential because they can transform into osteoblasts which are bone-forming cells and chondrocytes or cartilage forming cells. Most MSCs are obtained from bone marrow, adipose tissue or Umbilical cord blood. In orthopedical practice, autologous bone marrow derived MSCs are most preferred owing to its availability and high differentiation potentials. MSCs are delivered systemically by injection to the site of injury or can be seeded onto scaffolds used in surgical operations. Delivered at the site of injury, MSCs help rebuild the injured tissue by undergoing differentiation into the required cell type, and at the same time help manage the inflammation that arises at the site of tissue injury by releasing pro-inflammatory and anti-inflammatory cytokines.

MSC therapies have been used in numerous forms of musculoskeletal and orthopedical disorders such as non-union fractures, osteoarthritis and rotator cuff injuries. In fracture healing, MSCs play the role of osteoblasts and envisage the synthesis of the extracellular matrix. In the case of cartilage repair, MSCs begin to specialize in chondrocytes, which regenerate the cartilage and walls of a joint and provide the structure of the affected joint's surface.

Another example of biological therapies there is the usage of PRP in orthopedical surgeries. PRP is an autologous product; it is prepared from patient's blood and after processing through centrifugation, the platelets are concentrated. Such platelets also contain growth factors that include the platelet derived growth factor (PDGF), the vascular endothelial growth factor (VEGF or FGF-2) and the transforming growth factor- beta (TGF-β)-all of which are critical in all phases of tissue repair. PRP is normally administered directly into the affected area where it encourages tissue repair through stimulation of the cells, creation of new blood vessels and putting down of new matrix proteins.

PRP preparation requires spinning the whole blood to isolate the platelet and subsequently loading them concentrated in a plasma solution into the affected area. PRP platelet concentration can also differ and it is believed that higher concentration is more effective for regeneration. PRP has been applied across orthopaedic pathology such as tendinopathies, ligament lesions, muscular strains, and chondroma- Thies. For instance, PRP injection therapy is normally prescribed to patients with osteoarthritis in with view of triggering new cartilage formation, alleviate pain and inflammation.

Growth factors are peptides which act locally as mediators of cell growth and differentiation, as well as angiogenesis and tissue repair. Science of recombinant proteins in orthopaedic surgery

includes growth factors like bone morphogenetic proteins, insulin like growth factor-1 and fibroblast growth factor to facilitate bone healing and regeneration of cartilage. BMPs are especially valuable in spinal fusions and the treatment of non-union fractures because they possess a very high osteogenic potential converting stem cells into mature osteoblasts [9].

Most growth factors can be administered locally, directly through injection to the target tissue, incorporated into a scaffold for applications in tissue engineering or in conjunction with other biomolecules such as stem cells or PRP. The main actions they perform when it comes to tissue repair are to promote mitosis of the cells involved in repair process and to help orchestrate angiogenesis which is new blood vessels formation necessary for the supplying the developing tissue. The growth factors also regulate the inflammation process at the site of tissue injury as a means of ensuring the best environment for remodelling is created. The uses of biological therapies in clinical orthopaedic surgery are mainly directed towards the process of ossification and chondrogenesis. These therapies have been used in injured patients with fractures, osteotomies, osteoarthritis, and soft tissue lesions inclusive of tendinopathies and ligament ruptures.

In bone healing, biological therapies have employed in treatment to hasten the rate of union in the fracture and in situations where there is delayed union or non-union of the fracture. Bone healing is a process of forming and later modelling a callus at the fracture site, which is a mass of new bone tissue. There are beneficial for forming and restructuring the callus stem cells and growth factors because they enhance osteoblasts' production and their regulation. At times, these therapies complement the conventional surgical procedures techniques like internal fixing using plates and screws. In cartilage regeneration biological therapy is mainly applied in osteoarthritis and in other injuries of the menisci or chondral injury meaning damage to the articular cartilage in the joints. Cartilage tissue possesses poor self-healing ability for regeneration due to the fact that it is an avascular tissue that does not have very rich blood supply; hence, regenerative medicine is very useful. In patients with osteoarthritis or traumatic cartilage injuries, MSCs and PRP have been seen to stimulate new cartilage matrix formation thus alleviating pain and improved joint function.

In biological therapy applied in musculoskeletal related surgery assessment is done both on the physical and reasonable indicators. In the treatment of bone injury, the evaluation that is most frequently employed is radiographic, which is used for the assessment of the healing process of the fracture, as well as the formation of the callus and ultimately the union of the bone. Therefore, union time is the most vital parameter that defines the effectiveness of these treatments. It is worth mentioning that at times during experimental study, the different bone samples are subjected to histological examination in order to determine the quality or volume of the regenerated bone tissue [10].

In the cartilage regeneration, the arthroscopic grading and the imaging assessment
including MRI are utilized to assess cartilage architecture. They include physical characteristics of cartilage type and organization of the matrix as seen under the microscope after treatment with therapeutic agents.

However, for the assessment of the global success of biological therapeutic approaches patient-reported outcomes are fundamental. Such outcomes include pain reduction, -- joint mobilization, and recovery period. To assess the patient's view and satisfaction of the treatment the following Patient-reported outcome measures (PROMs) have been utilized in clinical trials: The Visual Analog Scale (VAS) for assessing the severity of pain and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) for evaluating joint function.

Results

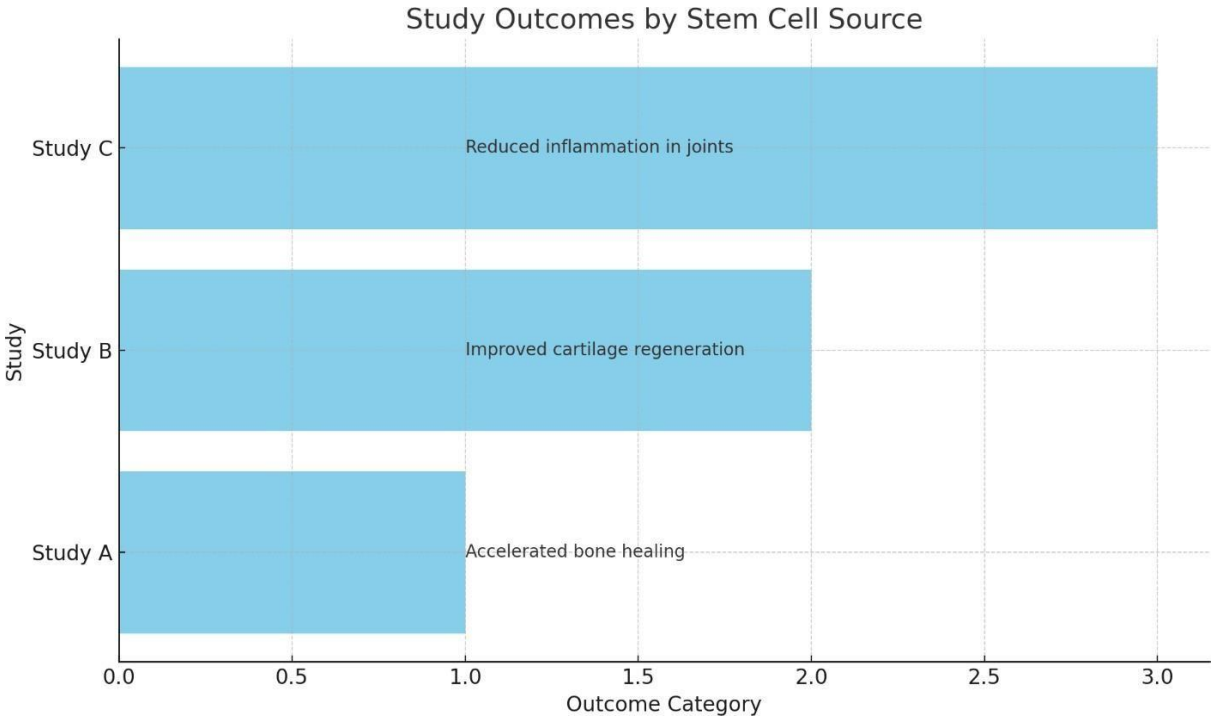
Mesenchymal stem cell-based therapies for bone and cartilage healing demonstrated considerable

potential of stem cell therapies. MSCs are not only capable of differentiating into osteoblasts but also into chondrocytes which has capability to form cartilage tissue. Scientific literature has noted various benefits associated with effects of MSCs for conditions such as non-union fractures, osteo arthritis and joint injuries.

In one clinical trial designed for patients with non-union fracture, outcomes of those patients who received injections of autologous bone marrow derived MSCs were compared with those subjected to conventional surgical procedures. The research established that patients that underwent stem cell injections experienced a faster rate of healing; with clinical images revealing faster formation of callus and remodelling of bone. In another study, adipose derived MSCs were introduced to patients with osteoarthritis of an advanced stage. These patients regained greater cartilage content, reduced inflammation and less pain with a significant increase in joint function.

Similar works have gone further in further substantiating how MSC therapy is better than conventional approaches. Mechanical fixation and physiotherapy are standard therapies aimed mostly at pain relief, and on the other hand, stem cells contribute to the healing of the damaged tissue. However, the followings issues still persist; variability of the cells, the best dosage, the routes of administration and so on. These aspects influence repeatability of outcomes, while further longitudinal trials are needed to assess viability of the regenerated tissues [11].

Study	**Stem Cell Source**	**Outcome**
Study A	**Bone Marrow MSCs**	Accelerated bone healing
Study B	Adipose Tissue MSCs	Improved cartilage regeneration
Study C	Umbilical Cord MSCs	Reduced inflammation in joints



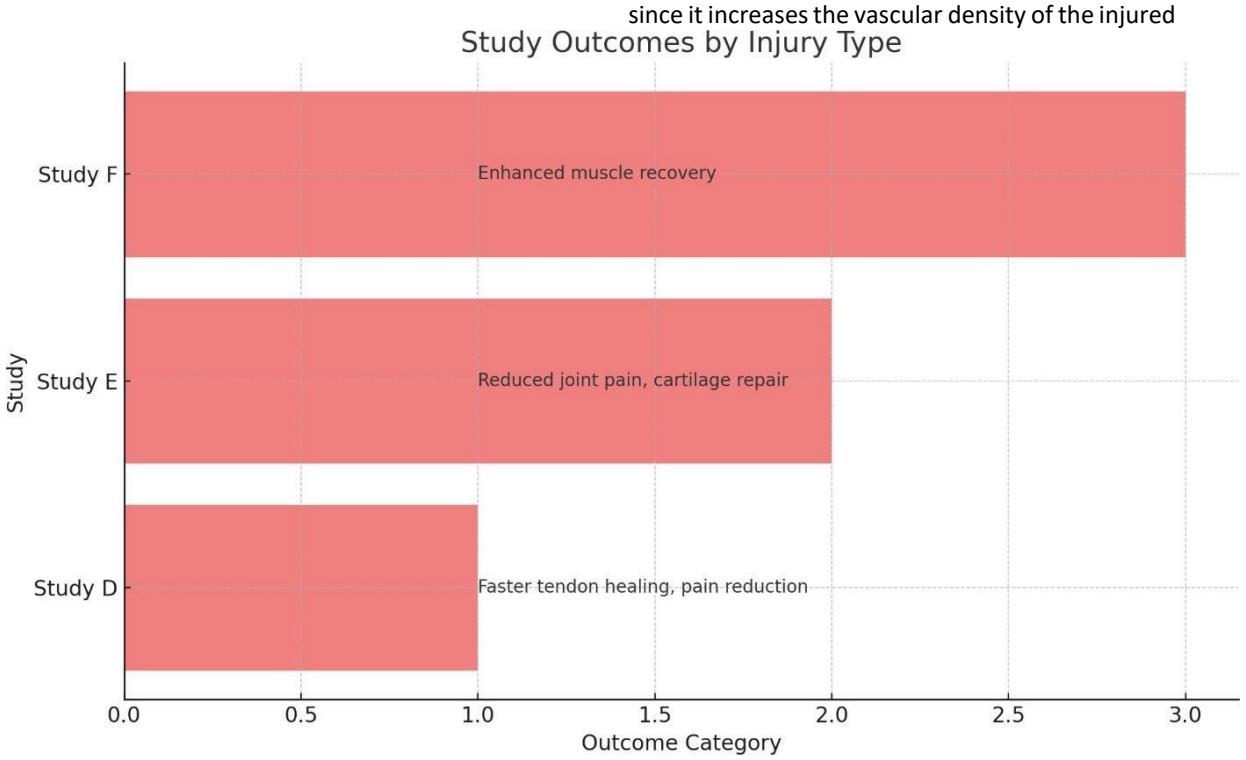
PRP is yet other biological therapy that has received uptake with time because of its effectiveness in promotion of tissue regeneration. PRP is filled with growth factors for example, PDGF, VEGF and TGF- β, all of which catalyze tissue repair through stimulation of cell divide and formation of blood vessels.

Research has supported its uses in different cases of tissue damages affecting tendons, bones and muscles, inflammation and strains. In a RCT to compare PRP with routine treatment of patients with tendon tear, the corresponding results showed significantly improved healing time with less pain. PRP was also discovered to contribute to muscle repair in athletes who suffered muscle pulls thus shortening the overall recovery time to the physical activity.

Specificity PRP treatment is highly recommended in osteoarthritis because it has actively helped to alleviate pain and inflammation. Another study finding on the same patients showed that osteoarthritis particularly the cartilage under went a boost PRP injections that revealed more advanced thickness of the cartilage matrix as seen from the MRI scans. This, PRP has an anti-inflammatory influence on the affected part, and this is supported by improved functional results, increased range of movements as well as decrease stiffness among the patients. However, some criteria which indicate the outcome of PRP therapy include the preparation method and platelet concentration. It's mainly due to the differences in the reported PRP variable and due to a lack of uniformity in reporting between studies. Furthermore, while PRP seams to give initial results, the effectiveness of the method in chronic pathologies such as osteoarthritis has not yet been demonstrated.

Study	**Injury Type**	**Outcome**
Study D	**Tendon tear**	**Faster tendon healing, pain reductio**
Study E	**Osteoarthritis**	**Reduced joint pain, cartilage repair**
Study F	Muscle strain	Enhanced muscle recovery

since it increases the vascular density of the injured



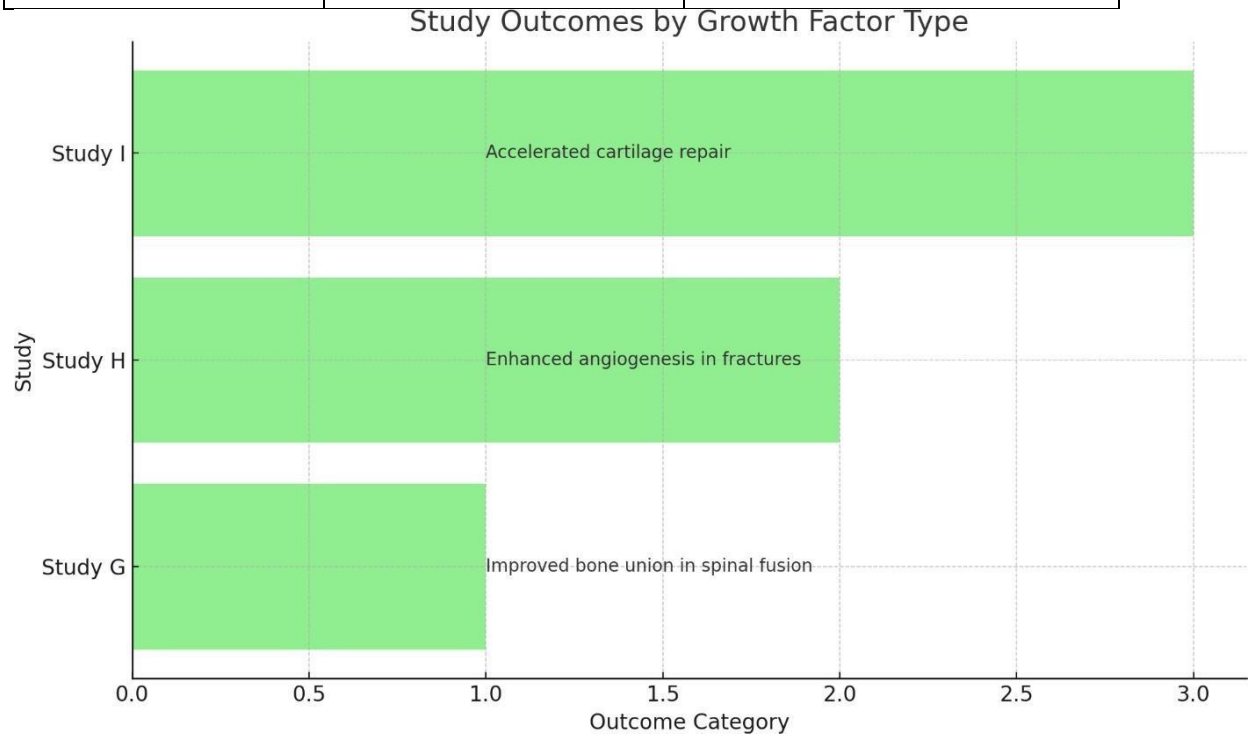
tissue.

Growth factors are proteins that control various cellular functions which are vital for tissue repair of damaged tissues – what includes proliferation, differentiation of cells, and extracellular matrix production. For orthopedic applications growth factors like bone morphogenetic proteins (BMPs), VEGF and TGF-β are used for bone healing and cartilage regeneration [12].

BMPs especially BMP-2, have been extensively reviewed in literature for bone regeneration particularly in spinal fusion and non union fractures. In clinical trials, recombinant human BMP-2 has been reported an efficacy of ninety-six percent in promoting new bone formation in spinal fusion surgeries among patient with no increased complication as compared to standard treatment. Also, it founds that VEGF is vital in stimulating angiogenesis since it is required to supply blood to the tissues that are recovering. VEGF application in fracture repair has also been proved to advance the formation of callus and the result of healing,

Whereas TGF-β has well-documented effects of high efficacy in cartilage repair. It evokes chondrocytes into active synthesis of the formation of the necessary extracellular matrix for cartilage repair. When testing the TGF-β in cartilage injuries, it was applied together with PRP & MSCs to promote the healing process. There was enhanced joint function as well as less pain among the patients that were given this duo therapy. It is, however, pertinent to point out that the various growth factors have potential in tissue repair despite various shortcomings. For example, the price of the growth factors, especially BMP-2, is still fairly steep, and the use in clinical settings may prove to be impossible. However, growth factors, more specifically, BMP-2 has to be administered with strict control; otherwise, it results inside affects such as ectopic bone formation. More work is being done to focus the growth factor therapies and make them better known in terms of safety as well as the costs.

Study	Growth Factor Type	Outcome
Study G	BMP-2	Improved bone union in spinal fusion
Study H	VEGF	Enhanced angiogenesis in fractures
Study I	TGF-β	Accelerated cartilage repair



These are therapies that have Stem cells, PRP and growth factors explained to combine the functions of the therapies in order to achieve the best goals of tissue regeneration. For instance, stem cells offer the important building block for the growth of tissue; PRP and growth factors on the other

hand, help to foster the setting for new cell development as well as the prevention of inflammation. Literature review evaluations have shown that multiple agents work better than single agents in clinical trials. For instance, comparative analysis of the outcome of treatment employing a combination of BM- deployed MSCs, PRP, and BMP-2 for non- union fractures established higher rates of bone healing, better callus formation, and enhanced structural features of bones regenerated by these agents compared to the outcome achieved when employing one of the agents. In cartilage repair the co administration of MSCs, PRP and TGF-β was significantly improved cartilage regeneration which is reflected from the clinical improvement in joint pain and function in patients suffering from OA.

With such benefits, combination therapies have large potential when it comes to use, but at the same time they port a number of complicating issues and high costs. The practicalities of harvesting, purifying, and transporting several biological products can be challenging, and the prohibitive costs of such treatments make them relatively expensive. However, more work is needed in order to discover precisely which biological agents work best when combined together, as well as which methods of administration have the greatest chance of producing predictable results.

Still, there are few difficulties and disadvantages of using biological therapies in the course of orthopaedic surgery. This is one of the primary problems of the reviewed studies since treatment protocols tend to differ considerably. Variations in the origin of the cells, the processing of the cells, the number of cells to be given and how they are delivered make relative results and defined procedures hard to set. These therapies also depend on the specific characteristics of the patient including the age and other of medical co morbidities and more importantly the type of musculoskeletal injury.

One is that, in many of the published articles, the follow-up time is not sufficient enough and thus we have little long-term data on the impact of these factors. The existing studies demonstrate the effectiveness of biological therapies in the short term and their long- term effectiveness is still under debate. More long-term evaluation of the outcomes should be conducted to evaluate the stability of the recreated tissues and possible side effects of these treatments, including the immune response or the formation of neo tissue. Last, the high cost of biological therapies is the factor that still hinders the possibility of vast use of these remedies. Depending on the location, the cost for harvesting stem cells, preparing PRP and subsequently administering growth factors can be very expensive and insurance companies do not fully cover the costs of such treatments. More research has to be done on the cost effectiveness of such therapy with the aim of decreasing their cost and making these therapy accessible to a larger population of our communities [13].

Discussion

Biological agents have taken incredible importance in the orthopaedic surgical procedure including stem cells, PRP, and growth factors in dealing with orthopaedic injuries instead of the conventional methods such as surgery and mechanical repair. Furthermore, each of these therapies reveals its benefits in different clinical situations; however, the primary purpose of all these therapies is to increase the body's ability to restore damaged tissues [14].

Stem cells derived especially the mesenchymal stem cells MSCs hold a lot of promise in both bone healing and cartilage regeneration because of their plasticity. They have the potential to transform into several varieties of tissue cells, including osteoblasts which are responsible for bone tissue and chondrocytes that is responsible for cartilage tissue. HSCs are often most effective in surgical treatment of compound and non- union, as well as in osteochondral lesions in which traditional therapies are not highly effective. PRP therefore works differently through the provision of a concentrated source of growth factors obtained from the patient's blood and acts to enhance the healing of soft tissue, reducing inflammation and

improve the repair of cartilages in arthritis which is mainly characterized by osteoarthritis. Some growth factors include bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β) which are signalling molecules that can control cellular processes of tissue repair with major relevance in bone healing indicators such as spine fusion or serious bone fracture [15].

In the context of regenerative medicine both of these therapies can be seen as huge steps forward in the treatment of musculoskeletal injuries. Conventional ORT seeks to give structural integrity back to damaged tissues to allow the body's healing mechanism to take root. Nevertheless, biological therapies surpass this by participating in the actual action of the healing process starting from the cellular level, not to mention the increased rate of tissue regeneration and improved cellular quality. Stem cells play their part by providing cells to replace the injured ones, while PRP and growth factors provide a signal for the healing of the tissues. Taken together, these therapies afford one a chance to step from mere symptom control to actual tissue reparative processes [16].

That is why the processes through which stem cells, PRP, and growth factors affect bone healing and cartilage regeneration are in relation to the cellular repair of the body. Indeed, stem cells including the multipotent MSCs develop into the lineages of the cells needed for bone and cartilage formation. MSCs when administered to the site of the lesion in an animal body, MSCs move to the injury site to respond to a signal on the microenvironment. In addition to osteoblasts or chondrocytes, they also commit to a variety of cytokines and growth factors that are important in regulating inflammation and tissue healing . By offering new cells, and encouraging tissue repair, stem cells offer a level of power in orthopedics that is unmatched.

PRP's action mainly depends on the capacity to provide a burst of growth factors PDGF, VEGF, and TGF-β directly to the affected area. These growth factors are crucial for initiating cell activities all of which include creation of new blood vessels (angiogenesis), cell division, and synthesis of extracellular matrix. This causes the area to have the right conditions needed to promote quicker healing and this is especially important in tendinopathies muscle tears, inflammation of the joint resulting from osteoarthritis. The high concentration of platelets in PRP also assists in controlling inflammation, which is just as relevant to early stages of tissue healing."

BMP's such as BMP-2, -4, -6 and- 7 and VEGF are involved in growth response mechanisms that are comparatively more related to the signalling pathways related to bone and cartilage healing. BMPs are members of TGF-β super family and play critical roles in differentiation of MSCs to osteoblast allowing their specific use in bone regeneration applications. VEGF is on the other hand essential in the improvement of blood flow to the affected site essential in delivery of oxygen and nutrients to healing tissue. These growth factors not only promote new cell formation but have roles in managing the remodelling phase of wound healing to guarantee that the new tissue developed is not only healthy and fully functional, but also properly and firmly constructed [17].

There has been an uptick as to the application of biological interventions in Orthopaedic surgical procedures with a tendency of altering treatment plans, especially because the strategies developed are unique to the patient. Unlike the aggressive conventional treatment regimens, the biological therapies are somewhat more individualised in terms of the kind of therapy given, the type of injury, the age of the patient and the general condition of the patient. For instance, patients with a younger age that also present with a higher reactivity to regeneration, may greatly benefit from stem cell solutions that have a high likelihood of promoting the repair of a fracture or cartilage lesion. On the other hand, patients that are older with degenerative conditions such as osteoarthritis are likely to benefit from PRP injections that have an anti-inflammatory effect and improve cartilage healing. Perhaps the most important aspect as far as clinical application of the above therapies is concerned, is the fact that it enables clients to

recover faster. Stem cell therapy in non- union fracture has been seen to reduce the period taken by the bones to knit faster meaning that patients with such fractures can go back to their daily activities much earlier. Likewise, PRP injections have shown shorter recovery time in soft tissue injuries and they are thus preferred by athletes. Moreover, a good percentage of these therapies are non- surgical some are actually administered through injections; this decreases the likelihood of complex risky surgeries, which also entails lengthy healing periods.

Thus, while more data are still being gathered, achieving customized therapies according to genetic or molecular subclassification of the patient might be more realistically within reach. For example, patients who had markers for poor healing might be eligible for more biological interventions that brought together stem cells, PRP and growth factors to promote healing outcomes.

However, biological therapies in orthopaedic surgery are not without their problems as will be discussed as follows. Among those factors, the most significant inhibitory factor is that there are no uniform protocols in most centres. Since there are differences in PRP preparation (for example concentration), stem cell origin (bone marrow, adipose tissue, umbilical cord), or the dosage of the applied growth factors a direct comparison of the results of the individual studies is almost impossible. Such variability hinders the development of a consensus on best practice that allow for standardization of results across clinical contexts.

Also, the expense of the biological treatments like the stem cell and growth factor therapy is still prohibitive and still put as a big hindrance to the popular use of the therapies. Some of these therapies are not reimbursable by insurance and, therefore, affordable to only those patients who could benefit from such therapies. The high cost may be attributed by the processes with which the biological agents are harvested and prepared, not to mention that their use is regulated and therefore takes time to be introduced to the marketplace.

Subsequent studies should involve vast, randomised controlled trials because such therapies' effectiveness require stronger proofs. Long-term studies are being all the more crucial to gain insight upon the overall benefits which are needed to define the long- term impact for example whether the healing rate of bones is just faster in the short term, or whether the cartilage could be regenerated in the long run. Furthermore, the studies, examining the application of stem cells in conjunction with PRP and growth factors, are expectable in increasing the benefits of the interaction of these agents . As with ANY other therapies the timing, dose and route of administration of these therapies will also need to be fine tuned.

Biologics and tissues have many different regulatory requirements that may depend on the country in which the orthopaedic surgeon operates. In most parts of the world stem cell treatments are considered to be experimental and they can only be administered to persons who are participating in trials. Despite that the legal use of mesenchymal stem cells, platelet-rich plasma, and growth factors is rather limited, the FDA and the EMA have provided certain guidelines to the use of these products. That has in a way hampered the use of these therapies in normal clinical practice.

They also include ethical issues especially on the stem cells issue that has raised a lot of controversy over the last few years. Most of stem cells that are applied in orthopaedic surgical procedures constitute MSCs which are acquired from tissues of adults such as bone marrow or body fat However, a number of issues concerning stem cell application in orthopaedic surgery include the risk of abuse or unethical tissue harvesting especially in countries where the laws regulating stem cell research are comparatively lenient. That stem cells are taken in a proper manner and the patients are well informed about the therapy being offered to them is very important. Furthermore, as these therapies continue to gain popularity, there is potential threat where those therapies will be sold

to the public without the sufficient scientific evidence necessary, which is the expansion of clinics offering treatments with or without efficacy and safety. The public health management of these products will require that biological therapies undergo appropriate clinical trials and regulatory scrutiny to protect the consumer and the fidelity of the specialty [18].

Conclusion

Therefore, outcomes derived from the application of stem cells, PRP and growth proteins demonstrate their monumental role in treatment of bone fractures and cartilage defects. Mesenchymal stem cells MSCs have been used in the repair of fractures and regeneration cartilage tissue while PRP aids in repair of tissue due to the delivery of high concentration growth factors that reduce inflammation and promote high rates of repair in musculoskeletal injuries. The above growth factors such as BMPs and VEGF have been identified to be central to stimulation of bone formation and neo- vascularization. In clinical terms, these therapies are far more effective than conventional solutions for addressing orthopaedic problems and restore healing time, tissue health. Thus, the attempts to integrate this knowledge into practice require a meticulous approach concerning patient peculiarities, the best ways to deliver knowledge, and protocolisation. With reference to the future, there are indeed very high expectations; biological therapies could dramatically change the management of musculoskeletal injuries however, larger sample studies along with future long term research are required to enhance the therapeutic use and yield the greatest therapeutic benefits in orthopaedic surgery.

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