Chapter 8

Platelet-rich Plasma (PRP) in Orthopedics and Traumatology — Review

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Additional information is available at the end of the chapter

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Abstract

In the last few years various methods are being applied in the use of platelet-rich plasma (PRP) during treatment in different orthopedic disease and sports trauma. They allow improvement of local biological condition and regeneration of different types of tissues. PRP is a modern treatment strategy with worldwide recognition. There is a high concentration of platelet growth factors in small amounts of plasma. PRP and its various forms have become one of the best methods to support the healing process of various tissues. PRP is used in regenerative medicine, because it provides two of three components (growth factors and scaffolds) necessary for complete tissue regeneration. The particular reason for the appearance of lesions is important in order to select an appropriate treatment method and technical application. Main indications are acute and chronic wounds, pseudarthrosis, ligament and muscle injuries, some tendinopathies, osteoarthritis, chondral injuries.

Keywords: Platelet rich plasma, platelets, platelet growth factors, chronic skin wounds

1. Introduction

Platelet-rich plasma (PRP) is a modern treatment strategy with worldwide recognition. PRP was introduced in the 1950s and is currently used in multiple fields of medicine. There is high concentration of platelet growth factors in small amounts of plasma. This works for offering an "ideal environment" for tissue regeneration and is part of the so-called biological therapy. The PRP implementation is an autologous therapy, which eliminates the risk of blood-borne infections. PRP and its various forms has become one of the best methods to support the healing process of various tissues. The term „regenerative medicine" was introduced in the 1990s. Many studies related to stem cells, growth factors, and extracellular matrix support the development of this new treatment philosophy. It differs from classic tissue engineering,

where tissue regenerates ex vivo. Here, the major idea is regeneration of fully functional tissue on the spot, while damaged tissue is provided for by cellular elements and the process is managed by local factors. PRP appears to be the main source of autologous products in regenerative medicine and a true precursor and foundation of the healing process along with scaffold and stem cells [1]. PRP is used in regenerative medicine, because it provides two of the three components (growth factors and scaffolds), necessary for complete tissue regeneration. This review discusses the state-of the-art-studies on PRP action mechanisms in surgical and non-surgical implementation (treatment of tendon injuries, cartilage damage, muscle trauma, cartilage and bone pathologies, and wound healing).

2. Platelet biology

Platelets are blood cells formed during hematopoiesis. They are built from cytoplasmic fragments of the long extensions of megakaryocytes and are small, discoid, and anucleate cells [2]. These extensions are interwoven through bone marrow sinusoids and are fragmented by shear forces, thus forming new platelets in the blood [3]. Their circulating lifespan is 5-9 days and their major clearance mechanism is via Kuppfer cells and hepatocytes. This became known after discovering the lectin receptor on the cell surface [4]. It is known that the functional activity of platelets changes depending on their size and age, as younger and larger platelets demonstrate better hemostatic function unlike smaller and older cells [5,6,7]. Platelets measure from 1 to 4 μm in diameter and apart from being anucleated, they contain different organelles. They are discoid or ellipsoid in shape and have three distinguishable zones: peripheral or outer zone, organelle zone, and cytosol zone.

Peripheral zone – This is the outermost section and it contains antigens, glycoproteins and various enzymes. This zone connects the platelets with other cells and blood vessel linings. Large quantities of plasma proteins and coagulation factors are firmly attached to this surface. Inside the membrane there are proteins (mostly glycoproteins and a small amount of carbohydrates). This membrane contains a double-layer of phospholipids, cholesterol and glycolipids. Glycoproteins have a number of specific receptors for certain coagulation factors, such as GPIb (thrombin receptors) and the von Willerband factor. The GPIIbIIIa complex is formed from glycoproteins IIb and IIIa and it acts as a fibrinogen receptor. Platelet adhesion and aggregation is affected by those glycoproteins [8].

Organelle zone – It is built from a variety of structures: dense granules, alpha granules, Golgi apparatus, dense tubular system and open canalicular system, lysosomes and mitochondria.

The dense granules (or dense bodies) are dense structures containing 65% of the total platelet adenosine-diphosphate and adenosintriphosphate. Serotonin, pyrophosphate, antiplasmin and large amounts of calcium, necessary for platelet aggregation are also stored there [8-10].

Alpha granules contain various growth factors (platelet-derived growth factor— PDGF, transforming growth factor beta—TGF-b, etc.), and clotting factors. Many of the 30 bioactive proteins, playing a key role for hemostasis are contained in these granules; hemostasis is considered to be the first stage of wound healing [11,12].

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Upon platelet activation, internal membrane systems including the dense tubular system (DTS) and the open canalicular system (OCS) interact. By means of cellular membrane invaginations, the open canalicular system helps the communication between the endoplasm and the external milieu. The mitochondria synthesize ATP, which is functionally very important. Acid phosphatize enzymes, glucosamidase, and galactosidase are contained in the lysosomes. Many particles contain glycogen, thus storing energy for cells. The Golgi apparatus is part of the membrane system as well [8,13].

Cytosol zone - It contains microtubules and forms a circumferential zone around platelets. Microtubules are connected to microfilaments. This is how the platelet cytoskeleton is formed; it directs the cell's movement, eliminates secreted products, and retracts clots. Upon platelet activation microtubules could be seen in platelet pseudopods [8].

3. Functions of the platelets

Besides participation in hemostasis, platelets also have other functions. To obtain hemostasis, the interaction of three main mechanisms is necessary: vascular response, platelet activity, and clot formation. When platelets are not activated by various stimuli, they are present in blood circulation in a state of quiescence in disc-shape form. The variety of stimuli can comprise physical or chemical ones, or a combination of both. The sub-endothelial collagen forming in the wound as a result of trauma, along with the von Willebrand factor(vWF), are the main factors that activate blood platelets in vivo, as well as thrombin, adenosine diphosphate, or a combination of them.

In experimental conditions the major activators for the study of platelets are collagen, thrombin and adenosine diphosphate, as well as their synthetic substitutes and calcium ions. Integrin A2b1, glycoproteins complex Ib-V-IX (GPIb-V-IX), and glycoprotein VI (GPVI) are the main collagen receptors. The involvement of collagen by these receptors is done as follows: after the process of binding of von Willebrand factor to glycoprotein Ib (GPIb), the exposed collagen binds to glycoprotein V (GPV) in the same complex, thus slowing down the platelets for a time, sufficient to allow for the further binding of the integrin a2b1 and glycoprotein VI (GPVI) with collagen [7,14].

According to Mehta et al., tissue damage leads to vascular exposure. Thus activating platelets and forming platelet plugs and blood clots. This is how natural hemostasis is provided. This naturally occurring hematoms consists of 95% red blood cells, 4% platelets, and 1% white blood cells. An analysis of a platelet-rich clot shows significant differences in composition as compared to naturally occurring clot, with 95% platelets, 4% red blood cells and about 1% white blood cells [15].

Platelets also have non-hemostatic functions. In addition to their primary role in hemostasis, platelets participate in many non-hemostatic processes. Their secretion contains many different substances [16]. On their external layer, a number of surface receptors are arranged, including adhesion proteins, cytokines, and lipopolysaccharide [17]. Interesting is the fact that

platelets also release various substances depending on the stimuli, by which they are activated [16,18]. Alpha granules contain many substances with directly opposing activities. This implies the existence of a mechanism for specific release of only a specific content of the granule, which is possible, but this is still not well studied [19,20]. Inflammation, immunity, and tissue recovery are some of the most characteristic features of platelets [7].

4. Platelet-Rich Plasma (PRP)

The PRP as a concept can be represented as the volume fraction of blood plasma, where the platelet concentration is increased compared to the baseline serum level. In platelet rich plasma, besides platelet concentrate, small amounts of white blood cells are also present and other blood components as well. Ideal is a concentration of 1,407,640 cells in microliter (with a standard deviation of 320.100) [21]. This value corresponds to a number of platelets, approximately five times higher than the normal, nomber in the blood, which is usually in the range of 150,000 to 350,000 cells in microliter (approximately an average value of about 200,000 cells in microliter) [22].

Marx et al. suggest that in order to obtain effective treatment with PRP, the approximate number of platelets should be about $1{,}000x10^3$ platelets in microliter in volume of a 5 ml plasma [23,24]. Jacobson et al. studied the influence of higher than five times the platelet concentration and suggested that angiogenesis is initiated at concentrations of platelet rich plasma from $1{,}500x10^3$ platelets in microliter and continues up to $3{,}000x10^3$ platelets in microliter. Interestingly, at concentrations of $5{,}000x10^3$ platelets in microliter, inhibition of angiogenesis is observed. They reached the conclusion that additional laboratory studies are necessary to elucidate the optimal concentration for use with a particular pathology. Concentration of the platelets less than $300x10^3$ platelets in microliter is called "low", 300 -$800x10^3$ platelets in microliter is considered "moderate", and >$800x10^3$ platelets in microliter is called "high" [7,25].

The presence of white blood cells in PRP may affect its use, independent of the concentration of the platelets [26]. The presence of the layer of leukocytes has led to the current classification, which distinguishes a clean (without leukocytes) PRP, identical to the platelet rich plasma of Anitua, and PRP with leukocytes. Also present in the classification the fibrin-rich gel known as a clean, without leukocytes, platelet-rich fibrin, and platelet-rich fibrin with leukocytes or Choukroun type [27,28].

Ehrenfest et al. categorized the kits based on their fibrin and leukocytes content.

- Pure platelet-rich plasma (P-PRP): cell separator PRP, Vivostat PRF, or Anitua's
- PRGF;
- Platelet-rich and leukocyte-rich plasma (L-PRP): Curasan, Regen, Plateltex,
- SmartPReP, PCCS, Magellan, or GPS PRP;
- Pure platelet-rich fibrin (P-PRF) Fibrinet;

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- Platelet-rich and leukocyte-rich fibrin (L-PRF): Choukroun's PRF [27,29].

This classification, despite the various comments, is an important step towards the systematization of knowledge, which allows for more objective comparisons of the results of treatment. It is necessary in future therapy with PRP to choose the allegedly most appropriate kit for the particular pathology [29].

PRP is an autologous therapy, which stimulates the healing of tissues and positively influences the recovery processes. It ensures a high concentration of platelets in a small volume of plasma. Once platelets are activated, platelet aggregation occurs and the contents of their solid granules and alpha granules is released [30,31]. In order to release the growth factors of the platelets, PRP must be activated to start the clotting cascade. The activation of platelets in vivo is done in three ways: by adenosine diphosphate, via membrane phospholipids system (arachidonic acid), and by inducing the presence of thrombin [32]. In hospital and clinical conditions, the conversion of prothrombin to thrombin takes place by means of calcium dichloride and thus platelets are activated. Another way is by means of autologous or bovine thrombin [25].

In order for the platelets and the PRP to be sufficiently functional, they should be activated as with tissue injury. As a result platelets release their contents and a cascade of events is initiated. Normal collagen is repaired. Collagen repair consists of the following phases: inflammation, proliferation, and remodelling [33,34]. Each of these stages is needed to restore the normal function of the tissue.

The first phase may last up to three days. The growth factors are released during this phase. Then fibroblasts penetrate and initiate the second phase of wound healing. At this phase fibroblast differentiation and neovascularization are observed. During the third phase collagen matures and strengthens as this process may last over a year [33-35].

5. Cascade of wound healing

Wound healing is a complex process that comprises of a sequence of events, starting from the time of injury and lasting several months, which can be divided into three phases: inflammation, proliferation, and remodeling [10,36,37].

In the inflammatory phase is observed at the beginning of the cascade with the activation and aggregation of platelets and the formation of a fibrin matrix. With platelets degranulation, cytokines are released that guide the healing process. Leukocytes are attracted by the cytokines through hemostasis and migrate to the damaged area. The first leukocytes involved and responsible for the initial wound cleaning are the neutrophils, which eliminate the bacterial and cellular waste [36,38,39].

During the proliferative phase, which spans through the next few days, monocytes migrate to the wound area under the influence of chemical signals from growth factors. The differentiating of macrophages by circulating monocytes is observed. Platelet signaling and modulation function are also performed by the macrophages. Gradually, the damaged area is impover-

ished of platelets. The macrophages clean the area through phagocytosis and secrete factors responsible for the formation of granulation tissue from the fibroblasts. During this phase, angiogenesis also begins under the influence of growth factors and thrombin. With the recovery of vascular endothelial cells new vessels also develop. Endothelial cells are activated by thrombin, while a process of interaction is also ensured, which restricts the intensity of the formation of new vessels [40]. In this phase mesenchymal stem cells also emerge and their differentiation is performed in specific tissues such as bone, cartilage, or vascular tissues being determined by chemical signals [36,38,39].

At the time of the remodeling phase, contraction of the collagen and convergence of the edges of the wound is observed. Cell density and vascularization is reduced, excess matrix is removed, and the collagen fibrils are aligned along the stress lines, which increases the strength of the newly-formed tissue [10]. Accumulated granulation tissue remodels or slowly transforms into a specific tissue such as skin or bone [36,38,39].

6. Platelet growth factors

A number of growth factors are located in platelet alpha-granules. In order to be released into the injured tissue monocytes, neutrophils, fibroblasts, mesenchymal stem cells and osteoblasts need the chemotactic effect of an available growth factor. Platelet-derived growth factor (PDGF) produces such effect. This growth factor influences mitogenesis of fibroblasts and smooth muscle cells. PDGF improves the formation of fibrous tissue, assists in the three phases of the healing cascade, and also significantly affects angiogenesis and re-epithelialization. Another important growth factor is transforming growth factor beta (TGF-b). It impacts the connection between fibronectins. It influences cell migration, proliferation and replication, and is present during inflammation processes [41].

Chronic wounds' and endochondral ossification's healing processes are highly influenced by vascular endothelial growth factor (VEGF). It is active in angiogenesis, too [13,42]. The next factor taking part in the recovery of chronic wounds is epidermal growth factor (EGF). It also influences the mitogenesis of endothelial cells, fibroblasts, and keratinocytes [42]. Hepatocite growth factor (HGF) is located in various tissues (several types of epithelium, liver, lung, kidney and tumor). It affects tissue regeneration and possesses morphogenic, mitogenic, antiapoptotic, and neurotrophic qualities [38,43-46].

7. Application of PRP in the treatment of chronic wounds

The process of healing of skin wounds is very intense and includes a number of phenomena, such as hemostasis, inflammation, formation of granulation tissue, epithelialization, neovascularization, collagen synthesis, and wound contraction. Several studies demonstrate that the growth factors are depleted in chronic wounds. Platelets have a tendency to aggregate when activated, having a leading role in skin healing. Activated platelets release growth factors,

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adhesion molecules, and lipids through which migration, proliferation, and the function of keratinocytes, fibroblasts, and endothelial cells are regulated [47].

Skin wounds are defined as the absence of tissue, where epidermis and dermis are affected, while sometimes can reach the adipose tissue and muscle fascia. In this process, no natural regeneration is observed and tissue lesion is transformed into fibrotic scarring [48,49]. Skin wounds have a frequency of 0.78% and huge funts are spent for their treatment. Annually, 2% of the budget is used for health in the European Union (EU), £40 million in the UK, $-1.3 billion are used for the treatment of decubitus in the US [48].

According to Zhu et al., chronic cutaneous wounds are quite frequent in developing countries. They are difficult to treat due to insufficient amount of growth factors. Sometimes wound infections are observed. Conventional treatment with various known techniques and methods is not enough due to the insufficiency of growth factors. Dressing and surgical debridement is used for these patients, but these strategies do not lead to significant outcomes [50].

For the development of skin wounds facilitate various etiological factors such as: chronic venous disease, peripheral arterial disease, neuropathy, arterial hypertension, physical injury, hematologic disorders, skin infection, inflammatory diseases, neoplasms, iatrogenic changes, and those associated with nutrition [48,49,51].

PRP gel has been used for wound healing stimulation on molecular and cellular levels for the last two decades [48,52]. Martinez-Zapata et al. showed tissue regeneration in maxillofacial surgery, chronic ulcers, and surgical wounds in their systematic review [53]. Weglein et al. assessed studies dealing with diabetic wound healing and another study reviewed the healing of chronic wounds [24]. Carter et al. reviewed wound healing when PRP gel is applied and wound healing of control groups (conventional wound care) and reported on a number of indicators [48,52].

With these studies, it was observed that PRPs have effectively stimulated healing in wounds with delayed healing. In a study, Martinez-Zapata et al. reported that the percentage of full healing of wounds treated with PRP has increased compared to that of control wounds. Carter et al. performed a meta-analysis of articles for chronic wounds and support the idea that the use of platelet rich plasma favors full healing compared to control groups [9,19,43]. In a study by Villela et al., they reached similar conclusions, with one of their conclusions reaching so far as to conclude that PRP is the method of choice for the treatment of wounds [48,21].

Difficult to heal wounds are considered those that do not heal after the fourth week of their appearance after being treated with standard methods for the particular pathology. Chronic is a wound that is not healing for a period of three months. The evaluation of each wound is very important. For the purpose, a number of point scales suggested by Cancela et al. based on clinical and anatomical criteria for the size of the wound are used, while a patient variable is also taken into account. The points are randomly defined using clinical experience in wound healing. Common parameters are assessed such as the presence or absence of erythema and edema surrounding the wound, purulent discharge, presence of fibrin, swelling in pressure, swelling with ocher dermatitis, and granulation [48].

Anatomical features are noted and graded such as open bone or tendon, location of the wound, and quality of the pulse of artery dorsalis pedis and artery tibialis posterior (when related to wound location) [48]. Wounds are measured to determine their overall surface, depth, and distribution of undermining of the wound edges. The duration of the wound is determined by the history [48].

There are many studies relating to the pathophysiology of wounds. Skin wound healing is an intensive process and in it are observed a number of events such as hemostasis, inflammation, formation of granulation tissue, formation of new vessels, collagen synthesis, epithelialization, and contraction of the wound. The process of reduction of growth factors in chronic wounds is demonstrated in numerous reports as a result of their reduced production and release, sequestration, or degradation. These mechanisms can be combined [48,54].

Platelet aggregation has a clearly expressed effect in the process of skin wound healing. In this process, growth factors are released and, adhesion of molecules and lipids is observed, while they are responsible for the regulation of cellular migration, proliferation and function of keratinocytes, fibroblasts, and endothelial cells [11,55]. Platelets secrete several antimicrobial peptides when activated by thrombin. PRP has an important antimicrobial and immunoregulatory activity obtained from leukocytes [56,57]. A review of studies using different products rich in platelets demonstrates significant improvement in the treatment of chronic wounds.

Anitua et al. presented an open and randomized study to evaluate the effect of PRP in chronic ulcers of 14 patients. They reported good healing response in 80% of the cases after 8 weeks of treatment, compared with 20% in the control group. Leukocytes were not detected in the analyzed products. Their explanation for the good results lies in the high concentrations of growth factors [48,54].

Crovetti et al. monitored the evolution of chronic skin wounds in 24 patients treated with autologous or homologous gel (depending on the case) and observed a complete healing in 9 of them after an average of 10 applications, with a reduction of pain in all cases [48,49].

Marté-Mestre et al. reported the recovery of vascular chronic ulcers with the use of PRP in 12 of 14 patients for an average treatment period of 2.93 months (average of 0.5 - 7 months) [48,58].

Dellinger and Britton applied autologous platelet gel and reported positive results, with no complications and acceleration of the healing process (5 - 8 weeks) regardless of Pan size. A reduction of the risk of amputation and improvement of quality of life was observed [22,48]. PRP has the advantage of having no adverse effects [59].

Margolis et al. found in a retrospective group study with neuropathic wounds in diabetic feet greater efficiency in the use of PRP against the conventional therapies, with a more obvious effect in severe wounds [48,60].

PRP may be used for treatment of various chronic cutaneous wounds, especially when standard conventional therapy is not good enough and surgical treatment is not possible. It reduces the duration, cost of treatment and the hospital stay. These procedures may be performed in outpatient clinics. There is reduction of wound pain after starting the treatment,

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reduced risk of blood-borne disease transmission, wound healing is restored, and local immunity is activated [61,62].

8. PRP in osteoarthritis

Cartilage defects and the most common joint disease, osteoarthritis(OA), are characterized by degeneration of the articular cartilage that ultimately leads to joint destruction [50]. Several treatments for OA exist, including exercise, weight control, bracing, nonsteroidal anti-inflammatories, cortisone shots, and viscosupplementation. The biochemical environment of the disease process should be influenced in order to achieve better control of the symptoms. There is an imbalance between various cytokines resulting in the increased quantity of proteolytic enzymes leading to cartilage destruction [25,63 - 65]. The repair of damaged articular cartilage and bone defects represents a great challenge for the orthopedist because of the regenerative limitations of cartilage and the difficulty in obtaining an adequate bone substitute. Damages to the cartilage havess been treated by microfracture, debridement, and grafting procedures [42]. The results obtained by these techniques are so far unsatisfactory, and in most cases, these techniques result in deposition of fibrous connective tissue with low mechanical strength at the defect location [56,66]. Broad application of PRP is typical for oral, maxillofacial, and plastic surgery, while in the last few years there have been papers showing administrations in orthopedics and traumatology. When obtaining PRP, high concentration of growth factors in a volume unit is observed and acceleration of the regeneration process in the arthritic cartilage. Consecutively, PRP stimulates local cell activity. This technique is low-priced and has no side-effects or dangers for the patient [33,67].

The presence of concentrated growth factors modulates the phenotypic expression of chondrocytes. This improves their recovery. TGF-b plays a major role in the differentiation of stem cells into chondrocytes. Synthesis of cartilaginous matrix is improved, as well. PDGF and IGF are both key parts of the recovery process, as the first one stimulates proliferation of chondrocytes while the second one increases the synthesis of proteoglycan - macromolecules. Thus, the strength of cartilage is improved [30,56]. Not only does PRP stimulate cellular activity and the process of regeneration and repair, but it also improves bone and cartilage recovery when biomaterials are applied [68,69]. In order to recover cartilage defects, not only PRP is needed but also an adequate biomaterial that has similar characteristics as the natural tissue and promotes cellular adhesion, proliferation, and differentiation [56].

According to Hunziker et al., TGF-b increases chondrogenesis [24,70], while Kon et al. documented PRP amplification of chondrocyte proliferation with convincing clinical effects on degenerative knee OA [24,25,70,71]. Results of the Kon et al. publication on 115 arthritic knees treated with PRP showed improvement in the functional status and pain scores “which remained positive at 6 months, with only mild degradation of scores at 1 year”. It was also mentioned that lower grades of arthritis and younger patients had better outcomes [25,72].

Qi et al. shared results on the treatment of osteochondral defects in rabbits with PRP and biodegradable collagen scaffolds. PRP was put into collagen scaffolds (0.05 ml PRP/structure)

and then implanted in osteochondral defects (4 x 3 mm) produced in the patellar sulcus of rabbit femurs. Evaluation of tissues was completed after 6 and 12 weeks by histological analysis and a mechanical indentation test. The results in both follow-up times were improved and showed that PRP possesses the capacity to stimulate the regeneration of critical defects in cartilage [56,73].

According to Patel et al. in a study with level 1 evidence, PRP has a superior effect compared to placebo in patients with varying degrees of knee OA. They tested 78 patients (156 knees) and observed that PRP alleviated the symptoms of OA when compared with a saline injection used as control. Follow-up period was up to 6 months. The results showed that with the help of PRP, the homeostasis and function of the knee joint can be improved [74,75].

Wei et al. reported the effect of PRP on the regeneration of cartilage in vivo. Auricular cartilage chondrocytes from rabbits were added to PRP (5 x 10^7 cells/ml PRP), injected subcutaneously in the dorsum of the donor animal, and after 60 days the tissue was evaluated by magnetic resonance, histological, and histochemical analysis. The results exhibited cartilaginous tissue formation in those groups that were injected with chondrocytes and PRP. In the groups in which only PRP was injected, cartilaginous tissue formation was not

observed. The authors inferred that PRP is effective in stimulating regeneration of cartilage when associated with viable cells [56,76].

A level 1 study published in 2012 in the Journal of Arthroscopy by Sanchez et al. used PRP type 4A to observe the results of PRP injection compared with hyaluronic acid. In this study 176 patients, were randomized to receive three weekly applications of PRP (8 ml at weekly intervals) or hyaluronic acid injections. The study was well-conducted, but the results only focused on the short term (until 6 months of follow up). The study was awarded as the best randomized clinical trial (level 1) for 2012, which gives useful fundamental guidelines on how to study the effects of PRP [74,77,78].

In the light of orthopedic and trauma critical literature, there is no standardization of treatment methods, such that most of the works use 3–5 applications of PRP in intervals ranging from 1–3 weeks with no standardization of the amount of volume to be applied and the ideal platelet concentration method [74].

Important factors for results of PRP treatment are the amount of platelets, grade of chondrocyte damage, patient's physical activity, and medical history combined with psychosocial factors. It is good to investigate whether PRP balances anabolism-catabolism, and if there is, what effect of does the PRP have on the synovium. Given the patient's condition, appropriate PRP treatment in OA should use more anti-inflammatory cytokines instead of pro-inflammatory cytokines. The future of OA research aims at isolating cytokines contained in PRP termed as "autologous conditioned serum" to specifically inhibit IL-1 and TNF alpha and down regulate MMP-13 [25,79].

Early OA can be treated by implementing intra-articular PRP. Worse outcome is observed with patients of advanced age and disease process. Khoshbin et al. compared intra-articular administration of PRP to hyaluronic acid and non-setoroid injections and reported that

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sequential intra-articular PRP injections may have beneficial effects on adult patients with mild to moderate osteoarthritis for a period of 6 months [80].

Zhu et al. reported the fact that PRP contains growth factors, which may have a negative impact on the treatment of a joint with osteoarthritis. That is why those growth factors should be isolated. The following years may be focused on finding suitable and harmless growth factors to improve PRP outcome [50]. Dold et al. paid attention to the fact that there is insufficient data on PRP implementation on post-traumatic osteochondral defects. Further studies with long-term follow-up are necessary in order to illustrate the benefits of isolated PRP application or application in combination with surgical treatment when treating cartilage pathology [81].

9. Tendinopathies

Efficiency of PRP for treating tendinopathies has been vastly studied, and obtained results have been mostly positive (both in vitro and in vivo). Other research also supports the use of PRP for treating tendinopathies through testing cultures of equine and human cells [82,83]. An increase in the types of expression of collagen genes in tendon cell cultures with PRP was presented in a study by Schnabel et al [84]. Similar results were shown by Mishra and Pavelko in their study including an improvement in the pain felt by 15 patients with chronic elbow tendinosis after a single application of PRP [85]. In the PRP-treated group, 93% of the cases achieved pain reduction. Schepull et al. published the first randomized clinical study on the use of PRP in complete ruptures of the ankle tendon. Elasticity was evaluated after 7 weeks and functional assessments were completed after 1 year [86].

Creaney et al. in a recent study concluded that patients with resistant elbow tendinopathy were also considered appropriate for PRP treatment [87]. According to Peerbooms et al. in a double-blind study, with a level of evidence 1, the use of PRP in the treatment of chronic lateral epicondylitis was more favourable than injections of corticoids [88].

A significant statistic improvement at 1 year was observed in the group treated with PRP in comparison to the corticosteroid group that showed improvement only at the beginning. It can be inferred that in addition to conservative treatments, PRP provides a viable therapeutic alternative for refractory tendinopathies (as confirmed in a South Korean study in PRP treatment resulting in "increased cell proliferation, genic expression and synthesis of the tendon matrix in degenerative injuries of the rotatory cuff") [89].

Other findings include the successful use of PRP (alternatively to conservative therapies) in Achilles tendon injuries in conjunction with stem cells and with other various tendinopathies of 203 patients (epicondylitis, patellar tendonitis, hamstring origin (ischial tuberosity) tendonitis, plantar fasciitis, flexor carpi ulnarii tendonitis, pes anserinus tendonitis, biceps femoris tendonitis, iliopsoas tendonitis, athletic pubalgias, and biceps brachii tendonitis) whose status did not improve during conservative therapies [90]. Local infiltration with PRP was applied and 75% success ratio in patients was achieved. According to Virchenko and Aspenberg, and in another study by Eliasson et al. in Achilles tendon rupture patients, results are better with percutaneous suture, PRGF placement, and early load-bearing and mobilization [83,91,92].

10. Anterior Cruciate Ligament (ACL)

As a result of the growing popularity of growth factor treatment techniques, PRP treatment applications have increased for both soft and bone tissue therapies. Several studies include positive results from such treatments. Repair of ligament injuries was tested by Sánchez et al., resulted in better healing outcomes and fewer complications after applying PRP to 100 patients with ACL reconstruction [93]. Fixation of the PRPG graft was studied by Radice et al. and the results were evaluated using MRI images of the interior of the ACL graft and concluded a 48 % faster and completely homogenous repair of the PRPG graft in the experimental group [83, 94,95].

Controversial opinions are shared on the application of PRGF/PRP in the reconstruction of the ACL and posterior cruciate ligament (PCL), such as the degree of effectiveness in the integration of the graft into the bone tunnel and rates of graft maturation [29,94,96]. A statistically significant difference ($p = 0.023$) was found during stimulation of both ACL graft maturation and ACL graft-bone healing with PRP application [93]. After histological assessment of the ACL grafts with and without PRP, Sanchez et al. found "a significantly better maturity index for ACL grafts (12 pts vs. 14 pts, $p = 0.024$), and more newly developed synovial tissue enveloping the platelet treated grafts (77% of cases) compared to the control grafts without platelets (40%)" [93].

11. Muscle

The use of PRP in muscle injury treatment still hasn't been studied thoroughly in humans [74, 97]. There are a number of studies on the effects on muscle tissue. For instance, Shen et al. stated that the inflammatory phase of skeletal muscle healing was controlled by growth factors, macrophages, and COX-2 pathway products [90]. According to Sánchez et al. "the clinical benefits of the ultrasound-guided application of growth factor in physical therapy, electrotherapy, and isometric exercise" for athletes include "a decrease in pain and swelling, a complete recovery of functional capacities before the expected time, and regeneration of the muscle tissue according to ultrasound". No evidence of fibrosis and no recurrence of injuries were found in any of the treated athletes [65,98].

Nevertheless, there still have to be more studies necessary to define the efficiency of PRP in acute muscle injury treatment and to create adequate protocols for administration. The main reason is the insufficient number and low methodological quality of the current studies on the use of PRP in human muscle injuries [38].

12. Surgery and trauma (Autologous fibrin Glue)

The introduction of fibrin glue in repair techniques started in the beginning of the 20th century. Its main use remains within surgical interventions and undergoes constant modification for better results. Fibrin glue became the predecessor of contemporary PRP treatment [99].

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A number of studies show the benefits of fibrin and platelet combined treatment. According to Everts et al., the application of autologous platelet gel and fibrin sealant in total knee arthroplasty lead to "significant postoperative increases in hemoglobin rates, required less allogeneic blood, and had fewer complications during wound treatment", thus showing high efficiency of treatment method [100]. Levy et al. evaluated the hemostatic efficiency of adhesive fibrin in 58 patients (a control group and a fibrin treated group) undergoing total knee arthroplasty. Outcomes were significantly higher blood loss for the control group (24 patients needed blood transfusion versus only six from the treated group) and no ostoperative adverse events in the treated group [101]. Sánchez et al.'s findings show the recovery of 12 athletes treated for total Achilles tendon rupture (six received an association of PRGF), during which repair was completed significantly faster than that of the control group, needed less time to recover range of motion and to resume training [102].

It is estimated that few studies have examined PRP action during treatment of orthopedic trauma [67,103], which shows that common treatment was the combination of PRP with bone graft, bone marrow and various bone substitutes (tricalcium phosphate, hydroxyapatite bioceramics), as well as treatment with human mesenchymal stem cells in an osteoconductive environment (platelet gel application used to increase formation of new bone tissue through modulating and stimulating the healing cell mediators) [67,103-105].

Other studies represent the effect of biological material in the hemostasis after total substitution of the articulation. According to the results of "98 total arthroplasties of the knee, 61 received application of PRP in the intraoperatory period on the exposed tissue and on the closure of the wound at the end of the procedure". Conclusions showed significant acceleration of recovery and better overall mobility and quality of life in PRP treated patients. The reasons for such fast recovery were attributed to the direct PRP application on knee surgery after arthroplasties. This seals the tissue and takes platelets directly to the wound, where the regeneration process starts immediately [106].

PRP may be used on patients with factures or in cases of total arthroplasies. With the introduction of new cement–free implants, the use of PRP between the implant and the bone might speed up the osteointegration process and improve the implant fixation [38].

13. Conclusion remarks

In the last few years various methods are applied in the use of PRP during treatment in different orthopedic disease and sports trauma. They allow improvement of local biological condition and regeneration of different types of tissues. Without doubt the use of PRP is absolutely a treatment option. According to Werner and Cramer the platelet is the most important cell for the repair processes of the body [74].

Recently, scientific research and technology have presented a new perspective concerning the understanding of "orthobiologic" treatments and the healing process of lesions [38].

PRP treatment is widely applied in the last ten years, especially for stimulating coagulation. A number of studies show that platelets demonstrate other functions, too. They are connected to liberating bioactive proteins and growth factors. The bioactive proteins as well as the growth factors improve tissue regeneration and the process of healing. PRP is the first true biologic therapy that has hit orthopedics by storm. Its ease of use and generally high safety profile has made it a preferred option for the most of the physicians and their patients worldwide. When trauma of musculoskeletal system injuries occur healing takes longer periods of time, and frequently they do not recover completely. Fast and effective recovery is of particular importance for athletes. That's why all healing methods that accelerate the recovery process are fundamentally important. Many different pathologies can be treated with PRP.

The administration of PRP in athletes has been gradually introduced in everyday patients. This has become another option for treatment in addition to conservative options. A number of surgical manipulations can influence results in PRP treatment, such as grafts, medication, and physical therapy.

"Following recommendations of the International Olympic Committee (IOC), the local applications of PRP have been used in the treatment of mild to moderate lesions with no surgical indication, or during surgery" [107].

Main indications are acute and chronic wounds, pseudarthrosis, ligament and muscle injuries, some tendinopathies, osteoarthritis, chondral injuries. Almost all the surgeries carried out since 2007 have used PRP, whether in gel or liquid form [108].

PRP represents an autologous biological material as its action is directly related to general clinical conditions of the patient. The particular reason for the appearance of lesions is important in order to select an appropriate treatment method and technical application. However, standardization in PRP protocols and long-term follow-up should clarify some of the questions regarding the durability of these procedures and any possible modification that should be done to achieve better results.

Various additional new studies are necessary to further improve the results of PRP application in different pathologies. This will help with understanding the different stages of the healing process and demonstrate the potential of PRP treatment in everyday patients.

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