



The use of PRP injections in the management of knee osteoarthritis

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Received: 3 May 2018 / Accepted: 11 January 2019 / Published online: 13 February 2019

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Abstract

Osteoarthritis (OA) is a degenerative disease involving joint damage, an inadequate healing response and progressive deterioration of the joint architecture that commonly affects the knee and/or hip joints. It is a major world public health problem and is predicted to increase rapidly with an ageing population and escalating rate of obesity. Autologous blood-derived products possess much promise in the repair and regeneration of tissue and have important roles in inflammation, angiogenesis, cell migration and metabolism in pathological conditions, including OA. Utilising platelet-rich plasma (PRP) to treat tendon, ligament and skeletal muscle has shown variable results across many studies with the current evidence base for the efficacy of PRP in treating sports injuries remaining inconclusive. More uniformly positive results have been observed by various studies for PRP in OA knee in comparison to hyaluronic acid, other intra-articular injections and placebo than in other musculoskeletal tissue. However, methodological concerns as well as satisfactory PRP product classification prevent the true characterisation of this treatment. Thus, further research is required to investigate how leukocyte inclusion, activation and platelet concentration affect therapeutic efficacy. Furthermore, the optimisation of timing, dosage, volume, frequency and rehabilitation strategies need to be ascertained. For knee OA management, these concerns must be addressed before this promising treatment can be widely implemented.

Keywords Platelet-rich plasma · Osteoarthritis · Intra-articular injection · Knee · Repair and regeneration

Introduction

Osteoarthritis (OA) is a serious degenerative joint disease resulting from the degradation of articular cartilage, degradation and proliferative reformation of subchondral bone and a low degree of synovitis that leads to a reduced quality of life (QoL). It is a major cause of pain and disability in the elderly population (> 70 years) (Neogi and Zhang 2013). OA alters the normal joint metabolism favouring increased catabolism and decreased anabolism (Dhillon et al. 2017). Inflammation and vascular pathology, in combination with cell death, meniscal changes, bone remodelling and subchondral sclerosis, produces a vicious cycle of progressive joint degeneration. This can be exacerbated by excessive mechanical stress and

oxidative damage (Wruck et al. 2011). Moreover, under conditions of metabolic or cytotoxic stress, such as in ageing, autophagy can be upregulated, further decompensating homeostatic mechanisms (Lotz and Caramés 2011).

In OA knees (Fig. 1), chondrocyte senescence and loss of cartilage integrity are major features. There is an increase in the water content of hyaline cartilage, accompanied by corresponding decreases in proteoglycan concentration, length and aggregation, causing reduced cartilage stiffness and fibrillation of the cartilage surface. From this, cartilage proceeds to erode and deep clefts may form. Concurrently, morphological changes in subchondral bone are found. As synovial fluid infiltrates, the formation of subarticular cysts in the subchondral bone also occurs. Osteophytes (bony projections) are characteristic features of knee OA in non-pressure areas, caused by the flattening of bone from pressure in high-wear areas (Adatia et al. 2012).

Many interacting factors have a role in indicating the potential for the development of knee OA, although age is typically highlighted (Blagojevic et al. 2010; Michael et al. 2010; Heidari 2011; Silverwood et al. 2015; Driban et al. 2017) (Table 1). Primary care databases from a variety of countries have shown a higher incidence of knee OA than hip or hand OA

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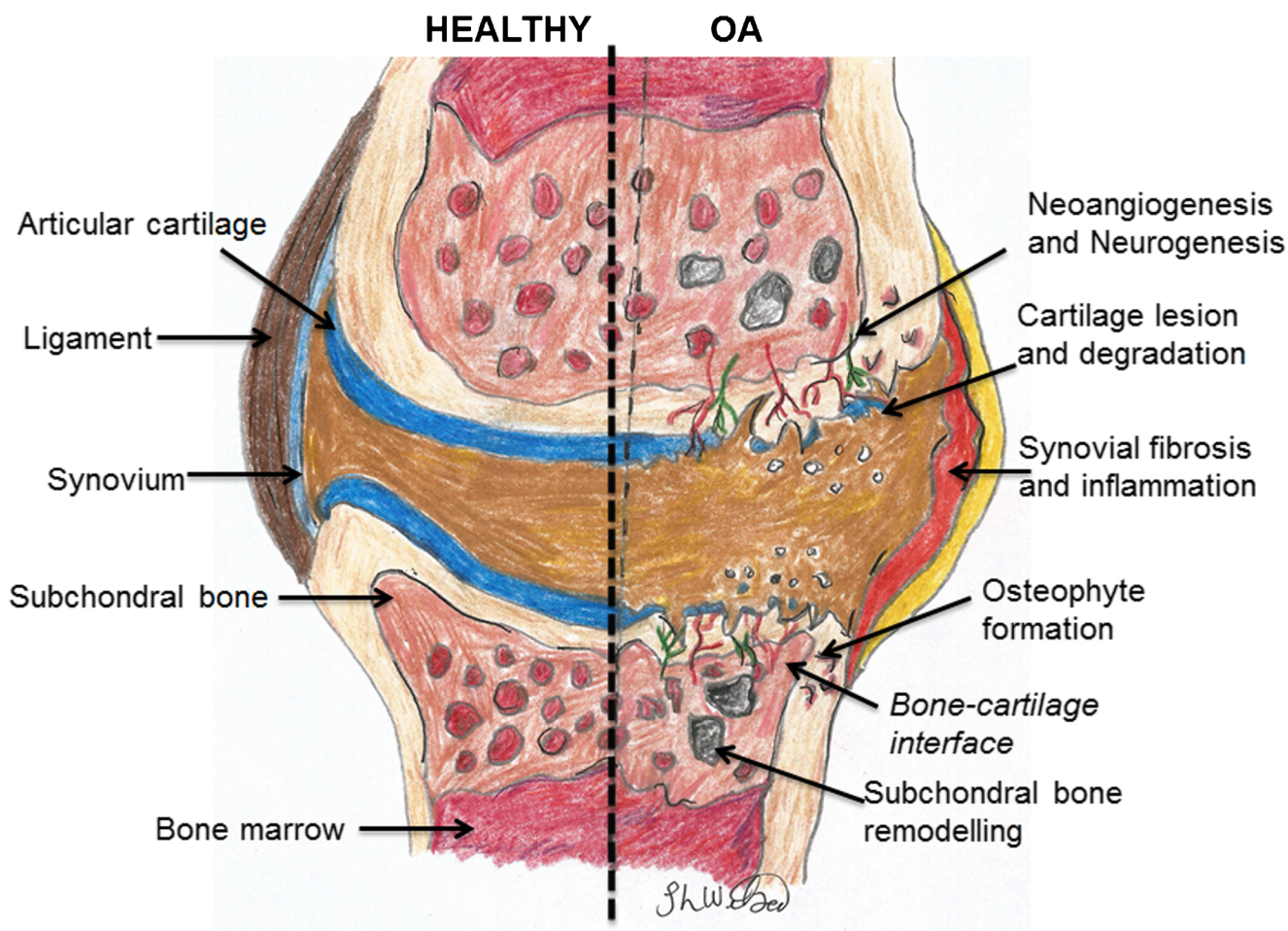


Fig. 1 Comparison of a healthy (left) and OA knee joint (right)

and a large increase in new knee OA diagnoses in the past decade, especially in 35–44 year olds (Prieto-Alhambra et al. 2014; Yu et al. 2015). Over a 7-year period, an estimated 13% of older adults (> 50 years) receive a diagnosis of OA with the knee joint implicated in 25% of the population (Jordan et al. 2014). There is also an accompanying socioeconomic burden in terms of cost of medical care for both government and individuals (Xing et al. 2017). It is a major public health problem worldwide (Pereira et al. 2011) and is projected to rapidly increase as the population ages and rates of obesity escalate (Cross et al. 2014).

Hip and knee OA has been ranked as the 11th highest contributor to global disability and 38th highest in years lived with disability (Cross et al. 2014). The disability associated with knee OA results in a considerable economic burden, both in direct costs related to treatment, particularly joint replacement surgery and job-related indirect costs, including loss of productivity (Murphy and Helmick 2012). Knee OA affects between 6% and 40% of the general population (Michael et al. 2010) and is significantly increased among retired elite athletes, with prevalence rates as high as 95% (Gouttebauge et al. 2015). The global burden of knee OA, as rated by the World

Health Organisation (WHO, 2011), is comparable with that of patients with cardiac dysrhythmias, liver cirrhosis or stage IV kidney disease (Mather III et al. 2013).

Current knee osteoarthritis incidence and management strategies

Knee OA management strategies include improvement in function, reduction in disability, pain relief and hence, improved QoL (Ng et al. 2012; Xing et al. 2017). However, there currently exist no pharmacologic agents that are able to halt OA progression or to reverse existing damage (Kanchanatawan et al. 2016). Existing approaches focus on preventing or delaying progression by developing less invasive procedures or applying interventions earlier in the disease onset (Zhang et al. 2008). Non-operative therapeutic interventions involving intra-articular injection at the knee joint, including hyaluronic acid (HA), corticosteroids, platelet-rich plasma (PRP), non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy and unloaded bracing, play major roles in the management of knee OA (Campbell et al. 2015).

Table 1 Risk factors for knee OA

Intrinsic	Extrinsic
Age	Previous trauma
<ul style="list-style-type: none"> • Advancing age effects of both sexes altered locomotor (stereognostic) control of opposing muscle groups 	<ul style="list-style-type: none"> • Macrotrauma • Repetitive loading (e.g., squatting) causing repetitive microtrauma • Increases risk 3.86 times
Sex	Co-morbidity
<ul style="list-style-type: none"> • Females more prone to develop Heberden's nodes, being female increases risk 1.84 times 	<ul style="list-style-type: none"> • Diseases such as: <ul style="list-style-type: none"> ▪ Cardiovascular disease ▪ Respiratory illness can contribute/accelerate progression of knee OA
Heredity	Body mass
<ul style="list-style-type: none"> • Heberden's nodes inherited as autosomal trait • Genetically determined metabolic disorders (e.g., ochronosis and Ehler-Danlos syndrome) predispose to OA 	<ul style="list-style-type: none"> • Overweight (BMI > 25) • Obesity (BMI > 30)
Ethnic origins	Resective joint surgery
<ul style="list-style-type: none"> • Increased incidence in European descent • Less common in Asians • Post-menopausal changes 	
Knee characteristics:	
<ul style="list-style-type: none"> ▪ Joint laxity ▪ Malalignment (femur-tibial angle (FTA)) 	<ul style="list-style-type: none"> Number of pregnancies (> 6) Muscle weakness

Modified from Adataia et al. (2012)

Platelet-rich plasma for inducing regeneration

PRP is an autologous mixture of highly concentrated platelets and associated growth factors and other bioactive components produced by centrifugal separation of whole blood (Fig. 2) that is used in orthopaedic and sports medicine practices to treat bone, tendon and ligament injuries (Fig. 3) (Sundman et al. 2014). The growth factors released by PRP have been discussed in great detail within the literature (Lubkowska et al. 2012; Pavlovic et al. 2016; Fernandes and Yang 2016; Parrish and Roides 2018) and have been shown to promote cell recruitment, proliferation and angiogenesis resulting in a reduction in the critical regulators of the inflammatory process and a decrease in the expression of inflammatory enzymes (Table 2) (van Buul et al. 2011). PRP may induce a regenerative response by improving the metabolic functions of damaged structures (Ficek et al. 2011; Chen et al. 2018) and has been shown to have a positive effect on chondrogenesis and mesenchymal stem cell proliferation (Kabiri et al. 2014).

In clinical practice, PRP is used to enable the application of autologous plasma and platelet-derived proteins to a desired location with the use of an appropriate scaffold to assist in the repair of the injured tissue (Marx 2001). The rationale for PRP in scaffolds is to take advantage of the huge amount of growth factors contained in platelets to promote cartilage regeneration; however, the use of PRP-augmented scaffolds is still in a preliminary state, with a low scientific level of power (Kon et al. 2013). In application to chondrocytes, growth factors promote matrix synthesis, cell growth and migration and facilitate protein transcription. The supra-physiological release of platelet-derived factors directly at the site of cartilage disease, particularly with interest to knee OA, may stimulate the natural regenerative signalling cascade and enhance the healing of tissue with further mediation of the anti-inflammatory response (Mascarenhas et al. 2014). In OA joints, PRP has been shown to affect local and infiltrating cells, mainly synovial cells, endothelial cells, those cells involved in innate immunity (such as macrophages) and cartilage and bone cellular components (Mifune et al. 2013; Dhillon et al. 2017). Additionally, PRP can affect inflammation and angiogenic processes and anabolism and catabolism balance in cartilage formation and alter the existing microenvironment during disease progression (Andia and Maffulli 2013).

The combined effects of PRP make it a potential option for management of knee OA, especially as a primary analgesic agent (Meheux et al. 2016). This is due to an increase in proliferation of tenocytes, osteoblasts, mesenchymal stem cells resulting in decreased pain levels postoperatively (Ogino et al. 2006). Despite encouraging preclinical results and increasing clinical interest, there remain multiple questions regarding the clinical application and efficacy of PRP, not least in the production of PRP, which can cause wildly varying characteristics. A simple classification was first proposed in 2009 following the fibrin architecture and cell content (pure PRP: leukocyte-poor PRP, leukocyte- and platelet-rich plasma; pure platelet-rich fibrin: leukocyte-poor platelet-rich fibrin, leukocyte- and platelet-rich fibrin). Each of these classifications had different growth factor release profiles (time, concentration) but studies found additional biological signatures and mechanisms within each family (Dohan Ehrenfest et al. 2014). A further classification can be included in the method of application (e.g., injections, glues) and the area of application (e.g., oral/maxillofacial surgery, skin wound healing). A more recent classification system called PAW (platelet, activation, white blood cells) is based upon absolute number of platelets, activation method and presence or absence of white blood cells (DeLong et al. 2012). According to the authors, the specific determination of the components of the PRP is vital in allowing comparisons between studies. In 2016, a further classification was

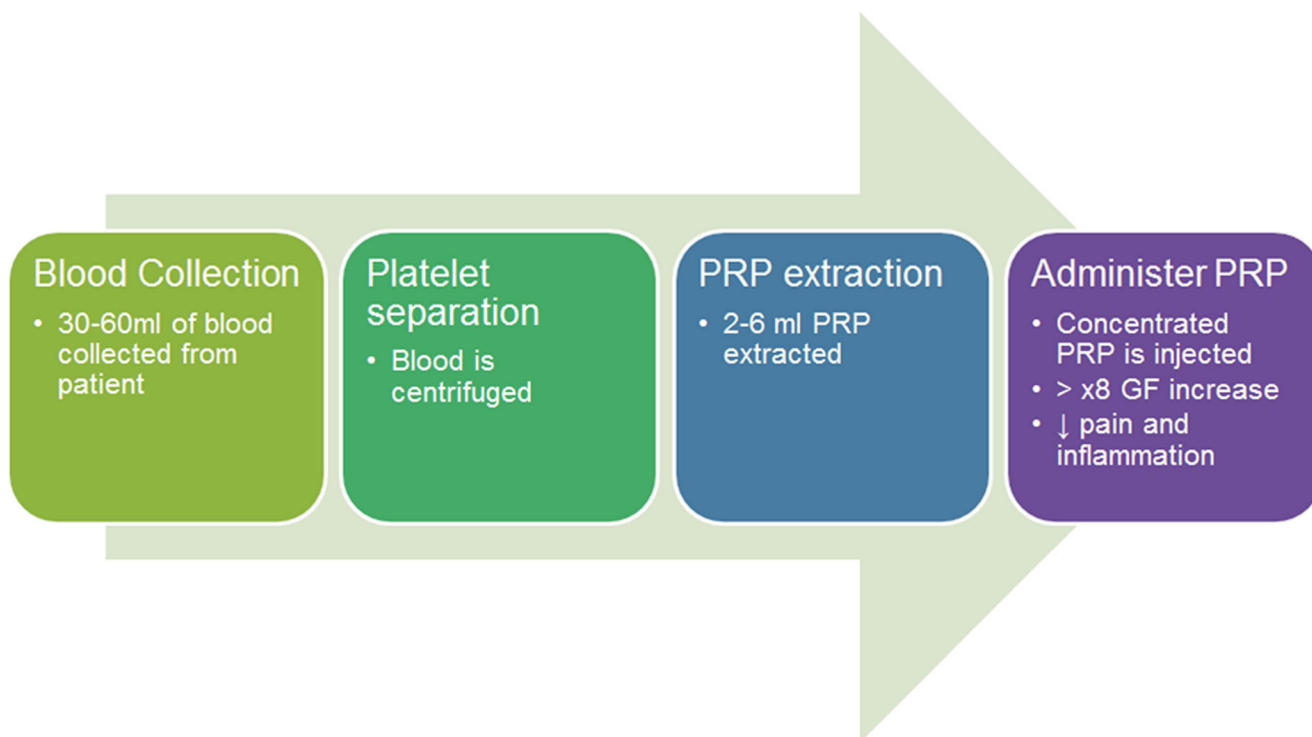


Fig. 2 PRP preparation process

proposed. Magalon et al. (2016) suggested that the dose of injected platelets, the efficiency of the production (percentage of platelets recovered), the purity of the PRP (ratio of platelets, leucocytes and red blood cells) and the activation process were overall termed the DEPA (dose, efficiency, purity, activation) system. Whilst each of these systems has their merits, as a product for application in the clinic, they must be able to be characterised by the administrator or be detailed on the product, in which case, the effect of storage/transport should be disclosed in studies and discussed further in the literature.

Current use of PRP in musculoskeletal tissues

PRP has been proposed as a promising biologic treatment with a wide range of applications in sports medicine (Lansdown and Fortier 2017). Injury type is significant, with benefits shown in the treatment of patella tendinopathy (Dragoo et al. 2014) and OA (Laudy et al. 2015) but not in Achilles tendinopathy or hamstring injuries (Manduca and Straub 2018). The available clinical studies on PRP as a treatment option suggest a good potential in favouring pain reduction and improved function for articular injuries to the ankle, knee and hip (Engebretsen et al. 2010). The evidence base for PRP across different injury types has been criticised for being inconsistent and uncertain (McNamee et al. 2018). In a meta-analysis,

Grassi et al. (2018) advocated PRP treatment as a safe procedure with negligible adverse effects that is readily available and has a minimal risk of reactivity compared to other exogenous compounds owing to the autologous nature of PRP injections. However, existing large and indiscriminate use of PRP injections for the treatment of acute muscle injuries in clinical practice is not justified by evidence (Grassi et al. 2018). Thus, caution should be applied to use in knee OA.

In muscle strain and tendon injuries, no statistical or clinically significant differences were found for RTP duration and re-injury rate, leading to the conclusion that PRP is no more effective than a placebo injection or intensive rehabilitation (de Vos et al. 2010, 2014; Creaney et al. 2011; de Jonge et al. 2011; Thanasas et al. 2011; Krogh et al. 2013; Hamilton et al. 2015; Reurink et al. 2015; Liddle and Rodríguez-Merchán 2015); however, other studies have pointed to enhanced recovery (A Hamid et al. 2014; Chen et al. 2018). Between these reports, significant differences in the quality of the study are noted and should be used as a guide when analysing knee OA efficacy.

In knee OA, PRP injections aim to stimulate cartilage repair and offer relief to other osteoarthritic symptoms, potentially delaying the need for joint replacement surgery. PRP injections have shown to influence the entire joint environment, leading to a short-term clinical improvement (Filardo et al. 2012a, b) with PRP injections being

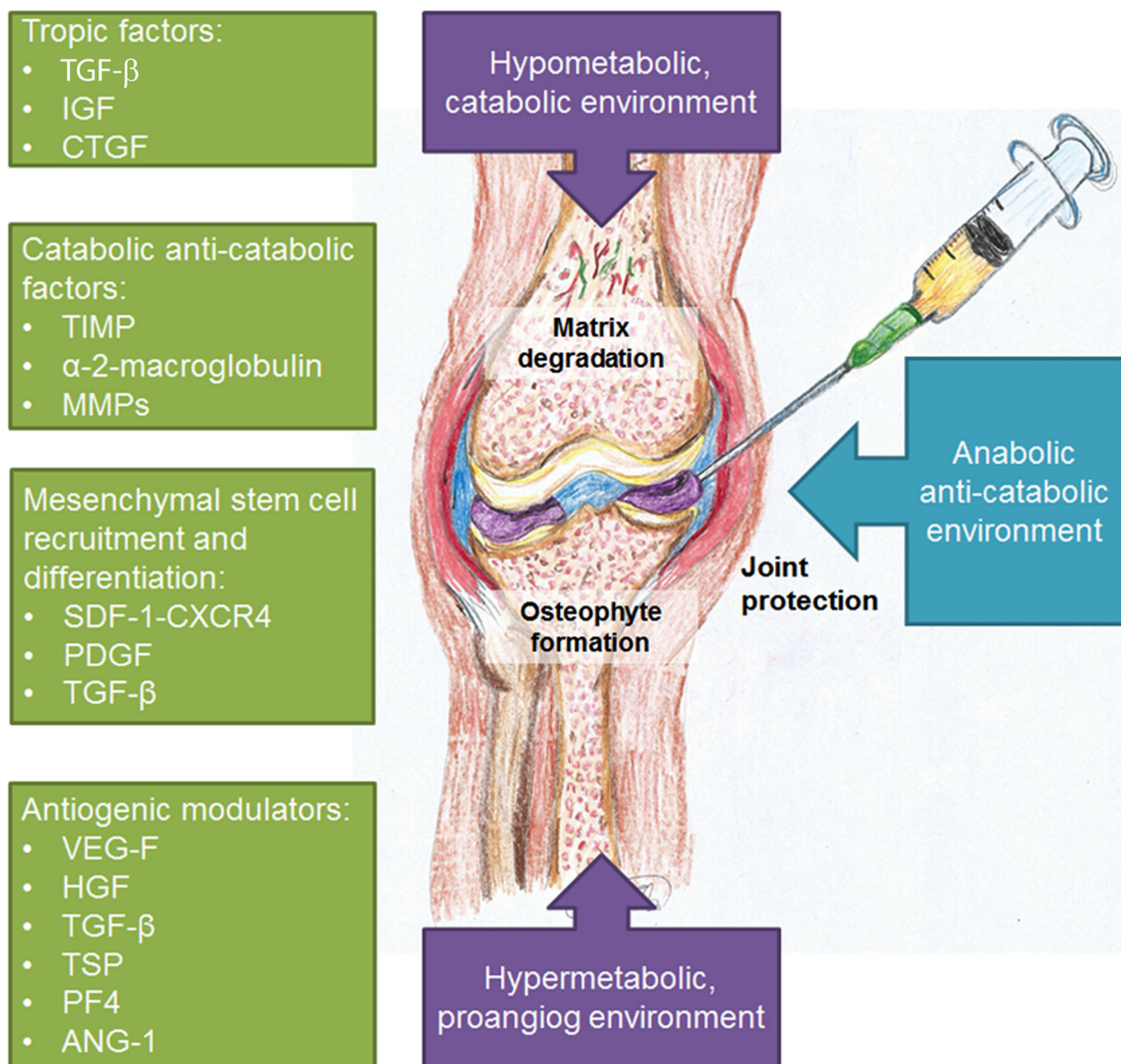


Fig. 3 Clinical applications of PRP

considered a safe procedure with more favourable outcomes when compared to alternative treatments (Laver et al. 2017). PRP is relatively easy to use due to its simple and rapid preparation and the minimally invasive administration requiring a simple intra-articular injection. Adverse effects are likely to be reduced due to the patient's own protein use and bioactive molecules can be concentrated to achieve the desired dosage, also eliminating potential drug interactions (Zhu et al. 2013). Without a synthetic element, PRP is, for the most part, not considered to be a drug or therapeutic substance and does not therefore need to fulfil the regulatory requirements needed for other biologic therapies.

PRP use in knee osteoarthritis

The use of PRP in the treatment of degenerative knee OA has increased in recent years given its apparent high margin of safety and ease of production and administration (Smith 2016). Contrasting scientific evidence exists regarding PRP injections for knee OA, with the efficacy of PRP injections widely reported (Rahimzadeh et al. 2018). The enhanced effectiveness of PRP for pain treatment and knee joint function in comparison to HA or placebo and positive outcomes in all stages of knee OA (early, middle and late), have all been reported (Kanchanatawan et al. 2016; Dai et al. 2017; Cole et al. 2017). In addition, the effects of PRP seemingly last

Table 2 Commonly discussed growth factors and effects associated with PRP

Growth factor	Effect
Platelet-derived growth factor (PDGF)	Angiogenesis; macrophage activation; proliferation and chemotaxis of fibroblasts; collagen synthesis; enhanced proliferation of bone cells
Transforming growth factor- β (TGF- β)	Fibroblasts proliferation; synthesis of type I collagen and fibronectin; deposition of bone matrix; inhibition of bone resorption
Platelet-derived epidermal growth factor (PDGF)	Epidermal regeneration; promotes wound healing through stimulation of keratinocytes and dermal fibroblasts proliferation; enhanced production and effect of other growth factors
Vascular endothelial growth factor (VEGF)	Vascularisation; stimulation of vascular endothelial cells
Insulin-like growth factor 1 (IGF-I)	Fibroblasts chemotaxis; protein synthesis stimulation; enhanced bone formation
Platelet factor 4 (PF4)	Enhanced influx of neutrophils; chemoattractant for fibroblasts
Epidermal growth factor (EGF)	Cellular proliferation and differentiation
Hepatocyte growth factor (HGF)	Inhibition of NF- κ B transactivation activity; anti-inflammatory action through inhibition of monocyte-like chemotaxis
Stromal-cell-derived growth factor-1 α (SDF-1 α)	Supports primary adhesion and migration of progenitor cells

Modified from (Engebretsen et al. 2010)

longer and are superior in comparison with intramuscular injection therapies (Prieto-Alhambra et al. 2014). Comparisons between intra-articular injection of PRP and placebo and HA therapy in mild and moderate knee OA have generally shown higher clinical outcome scores with PRP use (Filardo et al. 2012a, b). Similarly, using meta-analysis to compare the efficacy of PRP injections against placebo or other therapeutic means for the treatment of knee OA (Bennell et al. 2017) has reported greater pain reduction (Laudy et al. 2015) and functional improvement (Chang et al. 2014) with the use of PRP. However, this is at the expense of an increase in nonspecific adverse events (Khoshbin et al. 2013).

PRP use has been advocated as a treatment option in all stages of knee OA. Intra-articular PRP injections in active patients with knee OA show significant improvements in pain reduction, improved symptoms and QoL (Gobbi et al. 2012). This could be due to the immediate and sustained release of growth factors over a prolonged period, which enhances healing resulting in sustained clinical effects (Dhillon et al. 2017). Symptomatic relief for up to 12 months with increased benefits to patients with early knee degenerative changes has been found (Campbell et al. 2015) with significant improvements in function and reductions in pain with three injections per month yielding significantly better outcomes in the short-term (Huang et al. 2017). Improved pain outcomes after 3 months with a greater effect in lower OA grades have been reported (Montañez-Heredia et al. 2016). In moderate knee OA, functional status and pain have improved with a minimum of two injections (Kavadar et al. 2015). In late-stage knee OA, it may be that only a single PRP intra-articular injection is required to provide effective pain relief, thus

improving activities of daily living and QoL (Joshi Jubert et al. 2017).

Research into the efficacy of PRP has focused on comparing the effects of intra-articular PRP injections to other injection therapies. In many studies, PRP injections have improved functional outcomes when compared to HA and placebo controls and appear more efficacious in reducing symptoms and improving QoL (Raeissadat et al. 2015; Kanchanatawan et al. 2016). Kon et al. (2011) examined three homogenous groups of patients treated with three injections of PRP, low molecular weight HA and high molecular weight HA and concluded that autologous PRP injections have longer efficacy than HA injections and enhance articular function. The results showed improved outcomes for the PRP group at 6 months with younger and more active patients achieving better results with a low degree of cartilage degeneration (Meheux et al. 2016). Conversely, PRP causes a significantly greater acute inflammatory response and an increase in synoviocyte cell death (Braun et al. 2014) and induces more transient reactions than HA (Riboh et al. 2016). Spaková et al. (2012) compared three PRP injections with three HA injections in a randomised controlled trial (RCT) on 120 patients and discovered better Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and Numerical Rating Scale (NRS) in the PRP group compared to the HA group (Table 3). In a separate RCT with 120 patients, Cerza et al. (2012) compared four PRP injections at 1-week intervals with low molecular weight HA and observed better improvement of WOMAC scores at 24 weeks in the PRP group. No correlations with the grade of OA were found in either study. Additionally, better WOMAC scores were achieved at 24 weeks using PRP by

Table 3 Methods to assess impact of clinical intervention

Outcome measure	Function
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	Assesses pain, stiffness and physical function. Consists of 24 items divided into 3 subscales: <ul style="list-style-type: none"> • Pain (5 items): during walking, using stairs, in bed, sitting or lying and standing • Stiffness (2 items): following waking and later in the day • Physical function (17 items): stair use, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on removing socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, light household duties
Lequesne	Assesses the effectiveness of therapeutic interventions. Sections for index: <ol style="list-style-type: none"> 1. Pain or discomfort 2. Maximum distance walked 3. Activities of daily living
EQ-VAS	Patients' self-evaluation of overall health. 0 (worst possible health) to 100 (best possible health)
International Knee Documentation Committee (IKDC) Questionnaire	Subjective overall function score. Questionnaire looks at 3 categories: <ul style="list-style-type: none"> • Symptoms • Sports activity • Knee function Symptom subscale assists evaluation of pain, stiffness, swelling and giving-way of the knee. Sports activity subscale focuses on functions such as ascending and descending stairs, rising from a chair, squatting and jumping.

Sánchez et al. (2012) who examined 126 patients in a RCT with different grades of OA and compared three PRP injections at 1-week intervals with HA. Similarly, better outcomes have been documented when comparing PRP to HA groups at 6 months (Li et al. 2011; Say et al. 2013). Patel et al. (2013) compared normal saline with PRP and demonstrated that PRP significantly improved WOMAC scores following 6 months in comparison to the placebo groups, with patients experiencing benefits as early as 18 days. In a follow-up study, Patel and Dhillon (2014) hypothesised that the anti-inflammatory effect and chondral remodelling induced by PRP could be the reason for the improved clinical effects.

Limitations and recommendations for further research

Despite the apparent positivity in the use of PRP for treatment of knee OA, methodological concerns and considerable heterogeneity between studies are evident (Rodriguez-Merchan 2013b). Large RCTs are needed to further assess the efficacy and duration of PRP treatment for patients with knee OA (Rodriguez-Merchan 2013a; Lai et al. 2015). When planning or analysing treatments, frequency and number of injections,

as well as the activation methods (in the case of anticoagulated PRP), storage aspects, time from plasma isolation and accompanying therapy should be considered as at present they vary widely between groups. The greatest limiting factor for PRP use is the lack of standardisation with further research required to investigate how leukocyte inclusion, activation and platelet concentration affect therapeutic efficacy (Chen et al. 2018). Potential classification systems are discussed in depth by Dohan Ehrenfest et al. (2014), Lana et al. (2017) and Alves and Grimalt (2018). The cost-effectiveness of PRP, the demographic most likely to benefit and the optimal PRP protocol must all be researched further (Bennell et al. 2017). To this end, optimisation is still required regarding timing, dosage, volume, frequency, composition and post-injection rehabilitation (Engerbresten et al. 2010) and a unified classification needs to be agreed before this promising treatment can be widely implemented.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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