REVIEW ARTICLE

# Protocol for Optimising the Host for Favourable Outcomes of Platelet-Rich Plasma Therapy for Musculoskeletal Pain: A Review of the Literature

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## Abstract

Platelet-rich plasma (PRP) therapy has become a potential regenerative treatment for joint pain, particularly in the area of osteoarthritis and tendinopathies. Nonetheless, clinical results continue to be inconsistent, with significant inter-patient variability in response rates. Recent findings suggest that PRP bioactivity is strongly conditioned by patient specific biological and lifestyle factors. This systematic review aims to summarize modifiable patient-related factors that may be optimized before PRP therapy to improve platelet function, growth factor release, and clinical outcomes when treating joints for pain. A structured search of PubMed, MEDLINE, Cochrane Library and Embase databases was performed for studies investigating the effects of patient factors on PRP efficacy in musculoskeletal applications. We included studies published from 2010 to 2025.

**Keywords:** Platelet-rich plasma, osteoarthritis, joint pain, patient optimisation, regenerative medicine, growth factors, platelet physiology

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## Introduction

The burden of arthritis in the Asia Pacific has been described as 'massive' and joint pain is one of the most common chronic disabilities worldwide, with osteoarthritis alone estimated to be affecting 500 million people globally. The lancet conventional management options include pharmacotherapy and physical rehabilitation only partially control symptoms, whereas surgical treatments are associated with considerable morbidity but unpredictable long-term results. The consequent therapeutic void has stimulated much interest in potential treatments using regenerative medicine, including platelet-rich plasma therapy, which has shown promise as a treatment modality for knee OA.

PRP utilizes the body´s natural healing processes through harvesting a high concentration of autologous platelets and growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta(TGF-â), vascular endothelial growth factor(VEGF) and insulin-like growth factor-1(IGF-1), to induce tissue repair in degenerative joints while modulating inflammation. Clinical meta-analyses have shown

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that, following PRP injection for knee osteoarthritis, measurable changes in pain and function are possible, lasting 12 months or longer in responders[1,2].

However, the clinical outcomes of PRP therapy are surprisingly heterogeneous. Although a subset of patients shows significant and durable improvements, others exhibit a marginal or no response. Such variation has been linked with divergent PRP processing protocols, injection methodologies, disease severity and anatomical targets. However, increasing evidence demonstrates that biological mechanisms associated with the patient most of which are modifiable have major effects on PRP composition and therapeutic activity. The quality of PRP is largely determined by the components present at baseline levels in the patient, namely platelet count, platelet function as well as blood composition, which are utilized to derive these cells. Platelet biology and growth factor expression may be perturbed by metabolic derangements, nutritional deficiencies, systemic inflammation or lifestyle factors[3]. Therefore, a poorly controlled patient with diabetes, vitamin D deficiency, chronic NSAID use and active smoking may provide PRP which is biologically inferior to that provided by an optimized individual despite identical preparation protocols[4].

This recognition has prompted a paradigm shift towards systematic patient optimization prior to PRP therapy. Instead of presuming PRP is simply a biologic, clinicians are becoming more aware that treatment outcomes may be significantly improved by working on optimally prepping the "source material", the patient. This parallels decades-old principles in surgical medicine, where pre-operative optimization enhances outcomes across a broad spectrum of procedures[5,6]. This review summarizes the evidence supporting pre PRP health optimization strategies across domains in metabolic health, nutritional status, medication management, lifestyle change, comorbidity management and psychological preparation.

## Review of the literature:

We summarize the evidence to formulate best practice recommendations that clinicians could adopt to optimize successful PRP treatment in pain patients.

A) Optimising the patient by identification of pathology type, disease stage, chronicity, biomechanical factors, inflammatory status, and patient expectations is therefore essential prior to intervention.

A1) A careful characterization of the underlying pathology is vital because PRP is likely to be superior in degenerative and partially reparative conditions (e.g., early osteoarthritis, chronic tendinosis, enthesopathies and partial tendon tears) compared with advanced structural destruction, complete tendon rupture, severe joint deformity or end-stage bone-on-bone arthritis where residual regenerative capacity may be severely limited. Clinical examination and imaging modalities such as POCUS ultrasound or MRI that provide estimates of tissue viability, degree of degeneration, inflammatory activity/ neovascularization, and structural integrity[7,8]

A2) The chronicity of symptoms is also significant, since the natural history of many pathologies is associated with fibrosis, fatty infiltration or altered biomechanics, and central sensitization; these changes can induce a dampened responsiveness to regenerative therapies due to persistent inflammatory cascades[9]

A3) Biomechanical contributors such as malalignment, muscular imbalance, joint instability, poor kinetic chain mechanics and obesity should be identified and treated since continued aberrant loading will perpetuate tissue degeneration even in the setting of biologic augmentation[10]

B) Metabolic Factors Influencing PRP Efficacy

B1) Glycaemic Control and DM

Introduction Platelets are a unique type of cell that play an important role in cardiovascular complications[11] as well as contribute to many fields of regenerative medicine[12,13]. Hyperglycemia triggers several pathological modifications in platelets, such as increased aggregability, larger mean platelet volume, elevated platelet turnover, and impaired granule content[14]. Such changes compromise PRP quality and therapeutic potential directly.

Platelet dysfunction is accelerated by chronic hyperglycemia via a variety of mechanisms. AGEs

are known to accumulate on the membrane proteins of platelets which result in modified receptor function and dysregulated signal transduction cascades. Diabetes induced oxidative stress causes damage to the membrane of platelets and decreases alpha-granule content, which leads to a decreased reservoir of growth factors that may be released therapeutically. Diabetic patients also have increased platelet turnover, leading to a younger, larger, and more reactive population of platelets which will unexpectedly enhance uncontrolled growth factor release in an aesthetic application setting. In clinical studies assessing PRP results in diabetic versus non diabetic populations, the latter group consistently have much poorer outcome. In patients with diabetes, a large cohort controlled study of PRP for knee osteoarthritis revealed significantly reduced pain improvement at both 6 and 12 months follow up compared to best-matched controls. This effect was, importantly, dose dependent with worse outcomes observed for patients with higher baseline HbA1c levels.

B2) Obesity

Studies show that even a modest weight reduction (5–10% of body weight) achieves clinically significant amelioration in inflammatory markers and is also accompanied by improvements in metabolic indices[15,16]. A 12 week structured weight management program integrating dietary modification and exercise, is a viable approach for pre treatment optimisation of the energy profile of overweight patients in preparation for surgery. Notably, very low calorie diets provide an effective and fast way to gain weight, but such diets could lead to impaired immune function which you want to avoid right before PRP therapy. There was a linear association between BMI and response magnitude as each 5 kg/m² increase in BMI was associated with lower response magnitude.

B3) Metabolic Syndrome and Systemic Inflammation

Metabolic syndrome comprised of clustering central obesity, dyslipidemia, hypertension and insulin resistance is one of the most difficult scenario for regenerative therapy. These individual metabolic derangements act in synergy leading to combined negative effects on platelet activity and overall capacity for healing. Metabolic syndrome is characterized by mounted levels of inflammatory biomarkers including, but not limited to: C-reactive protein (CRP), IL-6, and fibrinogen representing chronic activation of pro-inflammatory pathways. This systemic inflammation changes platelet gene expression, granule content and activation thresholds. Clinical studies show that high-sensitivity CRP concentration above 3 mg/L is associated with lower PRP efficacy, indicating that inflammatory burden may be a modifiable target and prognostic factor[17,18].

An integrated approach to comprehensive metabolic optimization that addresses all components of the metabolic syndrome. Therapy is based on lifestyle modification, with a focus on adhering to the Mediterranean dietary pattern and increasing aerobic activity and weight management. The statin medications used in the pharmacologic management of dyslipidemia may have other pleiotropic (ie, non-lipid lowering) anti-inflammatory effects. Optimization of arterial pressure and treatment for sleep apnea (highly prevalent in the metabolic syndrome) close the metabolic priming[19].

In the pre-treatment assessment, fasting glucose has to be taken, as well as HbA1c, basal lipid panel and high-sensitivity (hs)-CRP. They have target goals such as HbA1c less than 7.0%, LDL cholesterol less than 100 mg/dL, blood pressure ascertainment 200 000/iL. Management of patients with recognized platelet dysfunction is required, but severe inherited platelet disorders may constitute relative contraindications to PRP therapy[20].

C) Enhancing the Quality of PRP through Nutritional Optimization

C1) Vitamin D Status

As Vitamin D deficiency has reached epidemic and pandemic proportions worldwide, the prevalence estimates range from 20% to 80%, depending on both population and thresholds. In addition to its well accepted role in calcium homeostasis, vitamin D has pleiotropic effects on immune function, inflammation and tissue repair that are directly relevant to PRP efficacy[21].

Platelets expresses vitamin D receptors and vitamin D status has a role on platelet functionality as genomic

and non-genomic actions. A lack of it has been linked to a higher tendency for blood platelets to clump together as well as changed patterns of growth factor expression. Additionally, vitamin D also has wide-reaching effects on the inflammatory response in target tissues, which may impact the regenerative environment to which PRP is injected[22].

Evidence suggests that vitamin D is relevant to PRP effects in the clinical context. In one study, patients with 25-hydroxyvitamin D levels below 20 ng/mL demonstrated a significantly lower improvement in VAS pain scores after PRP injection for knee osteoarthritis compared to vitamin D-sufficient patients[23]. Interestingly, response rates in cases with supplementation to achieve sufficiency prior to treatment were similar to those of naturally sufficient patients.

Assessment of vitamin D before starting PRP should be considered routine practice. Optimal serum 25-hydroxyvitamin D concentration, a standard marker of vitamin D status, should be between 40 and 60 ng/mL (100-150 nmol/L), which represents the upper range of sufficiency and is correlated with best immune and regenerative function. Individualized supplementation protocols according to baseline levels and supervised loading doses have typically been in the region of 50,000 IU weekly for 8 weeks before maintenance dosing of between 2000-4000 IU/day. Testing again at 8 weeks to confirm target levels have been achieved, before commencing PRP[24,25,26].

C2) Sarcopenia

Acute mass loss is a major biological driver in musculoskeletal medicine and has received increasing attention due to sarcopenia, the progressive loss of skeletal muscle mass, strength, and functional capacity[27]. Finally, a sufficient protein-rich diet and complete correction of sarcopenia before initiating platelet-rich plasma (PRP) therapy may have a positive effect on tissue healing due to an increase in muscle metabolism, mitochondrial function, collagen biosynthesis, and anabolic signalling pathways[28]. Reduced muscle mass plays a role in chronic low-grade inflammation, impaired biomechanics, joint instability, and prolonged healing due to its nature as an endocrine organ releasing anti-inflammatory myokines along with factors that are essential for tissue repair[29]. In addition, protein deficiency can affect fibroblast growth and extracellular matrix remodelling leading to impaired tendon healing that could further limit the regenerative potential of PRP[29,30]. Current evidence shows that older patients and those with chronic musculoskeletal pain frequently consume insufficient amounts of dietary protein, which in turn may lead to accelerated (sarcopenia) and lower rehabilitation potential. Pre-procedural optimization strategies that promote muscle protein synthesis, including high quality protein supplementation (1.2–1.6 g/kg/day), resistance training, leucine-rich exogenous amino acids and vitamin D correction . Protein is important for platelet production, generation of growth factors and repairing processes, so that it should be received adequately. Leucine is an especially important amino acid that activates mTOR-mediated protein synthesis. However, overt or subclinical protein malnutrition may limit the potential regenerative capacity with regards to PRP therapy[30].

Older adults with sarcopenia is a especially at risk population, where the decline in protein intake and anabolic responsiveness augmented by higher age translates into impaired regenerative potential. These patients frequently harbor comorbid joint pathology that would make them candidates for PRP yet demonstrate concomitant nutritionally compromised status[31].

Pre-treatment nutritional evaluation needs to assess protein intake with respect to demands. A recommended intake target for patients undergoing regenerative therapies is 1.2 to 1.5 g/kg body weight/d from sources of high-biological-value protein. Anabolic potentiation may be enhanced with supplementation (at doses between 3-6 g daily) of leucine-enriched essential amino acids. Ideally, nutritional optimization should be initiated a minimum of 4 weeks prior to PRP therapy[27,30].

C3) Iron Status and Platelet Production

Normal production of platelets in the bone marrow requires iron, and deficiency states of this element which can occur without frank anemia may

dramatically impair platelet quantity and quality. Thrombocytopenia and thrombocytosis, depending on severity and chronicity of the iron-deficient state, as well as functional and morphologic changes in platelets are associated with iron deficiency states [32,33].

In particular, iron deficiency anemia causes a challenging situation when it comes to PRP preparation. Lowering hemo concentrations leads to larger blood draw volumes needed to reach the same platelet yields, and iron deficiency itself likely has an independent impact on platelet function free from concentration effect. Platelets generated in a setting of reactive thrombocytosis, which is occasionally seen in iron deficiency, contain phenotypically different activation characteristics that may not be as therapeutically optimal[34,35].

Before PRP therapy, iron status should be evaluated with regards to serum ferritin, serum iron, total iron-binding capacity and transferrin saturation. Adequate iron stores for optimal platelet production are also considered to be reflected as target ferritin levels of 50 to 150 ng/mL with transferrin saturation greater than 20%. In patients with iron deficiency, oral supplementation (at least 325 mg ferrous sulfate ,65 mg elemental iron per day) should be started in advance of PRP therapy for at least 8 to 12 weeks prior to treatment. In cases of severe deficiency or malabsorption, intravenous iron repletion may be required[36].

C4) Omega-3 fatty acids and anti-inflammatory effects

Long chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have multiple mechanisms of action, resulting in their potent anti-inflammatory effects. These fatty acids compete with arachidonic acid as substrates for the cyclooxygenase and lipoxygenase enzymes, giving rise to eicosanoid metabolites that are less inflammatory. Furthermore, omega-3 fatty acids produce a unique class of pro resolving mediators (including resolvins, protectins, and maresins) that can actively promote resolution of inflammation and facilitate efficient repair[37].

The phospholipid composition of platelet membranes mirrors dietary intake of fatty acids, and omega-3 enrichment alters platelet function in a potentially therapeutically favourable manner for regenerative applications. Omega-3 supplementation attenuates platelet aggregation responses and induces a pro regenerative phenotype in the inflammatory profile of released mediators. The omega-3 index (EPA + DHA as a percent of erythrocyte membrane fatty acids) has been proposed as an inflammatory biomarker that is relevant to regenerative outcomes[38,39].

Considering pre-treatment omega-3 supplementation in all PRP candidates with special regard to patients who are either low in baseline intake or high in inflammatory markers should be recommended. Membrane incorporation is most meaningfully achieved with 2 to 3 gram combined EPA/DHA dosing, daily for at least an 8 week period. They should also be pharmaceutical grade fish oil supplements, which enables proper dosing and ensures purity. An omega-3 index can be measured to verify supplementation levels are sufficient (> 8%)[40,41].

C5) Antioxidant Status

As oxidative stress impairs platelet function and alters the facilitation of regenerative processes within osteoarthritic joints. Antioxidant nutrients such as vitamins C and E, selenium, and zinc have important functions in detoxifying reactive oxygen species (ROS) from the body and are needed for tissue repair process[42,43].

Vitamin C is implicated in collagen synthesis and immune function, both of which are pertinent to joint regeneration following PRP. It also causes a reduction in the tissue's response to stimulation by growth factors, and deficiency impairs wound healing. 500 to 1000 mg vitamin C supplementation daily, for 4 weeks before PRP therapy is sufficient, higher doses can induce pro-oxidant effects[44,45].

Zinc is a cofactor for many enzymes pivotal to tissue repair and immune function. Marginal deficiency is frequent, especially among older adult cohorts and patients with chronic inflammatory diseases. Measurement of serum zinc and supplementation to raise levels into the upper normal range may help ensure optimal regenerative responses[46].

D) Optimising Drugs

D1) Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs are the most important class of medications influencing treatment results with PRP therapy. These agents inhibit cyclooxygenase enzymes, preventing production of prostaglandins and thromboxane A2 necessary for initial phases of tissue healing as well as the activation of platelets. The anti-inflammatory mechanisms of NSAIDs that make them useful for alleviating symptoms directly counteract the biological mechanisms by which PRP exerts its therapeutic benefit[47,48].

Inhibition of platelet cyclooxygenase by aspirin is irreversible and remains effective for the remaining 8 to 10 day lifespan of the affected platelets. The non-aspirin NSAIDs produce reversible inhibition with a duration determined by drug half life from hours (ibuprofen) to days(naproxen, piroxicam ) Both mechanisms inhibit platelets in the PRP from activating appropriately and releasing growth factors after injection[49].

Studies investigating PRP in lateral epicondylitis reported that patients who avoided non-steroidal anti-inflammatory drugs (NSAIDs) for at least 2 weeks prior to treatment showed statistically superior improvement compared with those using NSAIDs recently or continued to use post-treatment. Similar findings have been reported in knee OA cohorts[50].

Discontinuation of NSAIDs before PRP is mandatory to achieve optimal results. We would stop aspirin for 10 days before treatment since this time should allow complete platelet population turnover. A non-aspirin NSAID should be stopped for at least 5 half-life (3 to 7 days for most commonly used agents). Patients that cannot remain without analgesia during this washout period should be switched to acetaminophen, because at standard doses it does not interfere with platelet function[48].

In particular, NSAID usage should also be prohibited in the weeks following PRP injection to allow the acute inflammatory response that is critical part of the regenerative cascade. Limitations Methodological issues affect the conclusions that can be drawn Most protocols recommend no NSAIDs for 2-4 weeks after injection, but some authors quote up to 6 weeks[49].

D2) Antiplatelet Agents

PRP biology is also significantly influenced by the use of non-aspirin antiplatelet agents used for cardiovascular indications. Clopidogrel, prasugrel and ticagrelor exert their antiplatelet effect by blocking the P2Y12 ADP receptor to cause profound and sustained platelet dysfunction. The combination of aspirin and a P2Y12 inhibitor with dual antiplatelet therapy poses an even more difficult clinical problem[51].

Individualized decision making with regards to antiplatelet therapy cessation prior to PRP based on cardiovascular risk is warranted. Temporary discontinuation can generally be performed safely with proper monitoring for patients receiving antiplatelet therapy for primary prevention or distant cardiovascular events (> 12 months). Modification of antiplatelet regimens in patients with recent coronary stenting, acute coronary syndrome within 12 months, or high-risk cardiovascular profiles warrants cardiology consultation[52].

For PRP therapy, aspirin should be halted for 10 days and clopidogrel for 7 days before if their discontinuation is considered appropriate. Prasugrel and ticagrelor have a shorter functional effect (disappears) and can be stopped at 7 days or 5 days respectively. Bridge therapy is not routinely recommended due to the low risk of thrombosis with short term discontinuation in carefully selected patients[53].

D4) Corticosteroids

Endogenously, systemic or locally administered corticosteroids have a wide array of suppressive effects on regenerative processes that could affect the results of PRP treatments. PRP-derived growth factors stimulate fibroblast proliferation, collagen synthesis, and angiogenesis processes that are inhibited by glucocorticoids. Local effects upon joints or periarticular tissues are particularly relevant, as residual drug may directly inhibit PRP function[54].

Prior timing of corticosteroid injection substantially affects PRP outcomes Clinical trial data have also

shown that PRP injection within 3 months of intra-articular corticosteroid administration yielded worse outcomes when compared to PRP without recent steroid exposure[55]. This was most evident by an interval of d 6 weeks[56].

Whenever possible, PRP delivery and corticosteroid injection should be separated by a minimum of 3 months. For patients on systemic corticosteroids, dose reduction or discontinuation (if feasible) should take place before initiating PRP. Low-dose maintenance corticosteroids (prednisone 5 mg daily or less) may be considered if discontinuation is not possible but patients should be counselled accordingly due to potential reduced effect.

D5) Proton Pump Inhibitors

New data indicate that proton pump inhibitors (PPIs), some of the most commonly prescribed drugs worldwide, may worsen both platelet function and PRP therapeutic effects. PPIs are platelet hydrogen-potassium ATPase inhibitors, and decreases the ADP aggregation responses in platelets. Furthermore, the well-established drug interactions between PPIs and clopidogrel (via CYP2C19 inhibition) imply wider effects on platelet biology[57].

Although there is still a relative lack of clinical evidence directly linking PPI usage to decreased PRP efficacy, the theoretical concerns regarding platelet function that lead clinicians to avoid their use should be heeded. In patients receiving PPIs for indications not applicable to PRP therapy (ie, "heartburn" without objective evidence of underlying pathology), a single 2-week interruption of PPI therapy is reasonable. Keep patients with documented gastroesophageal reflux disease, peptic ulcer disease, or Barrett's oesophagus on PPIs because the cardiovascular risks of withdrawal are probably greater than those associated with continuation[58,59].

D5) Anticoagulants

Anticoagulant therapy with either warfarin, direct oral anticoagulants (DOACs), or some form of heparin does not directly affect platelet function itself but adds practical considerations towards PRP therapy[60]. There may also be a slightly higher procedural bleeding risk (but this is usually low for regular joint injections). Even more so, patients on chronic anticoagulation tend to have challenging disease processes (such as atrial fibrillation or venous thromboembolism or mechanical heart valves) that further complicate medication management[61].

Given the low bleeding associated with PRP injection, anticoagulants should be continued for most patients. If this is warranted, the revised/evidence-based medication plan for patients undergoing endobronchial biopsy should be worked out with the prescribing physician and in line with current periprocedural anticoagulation guidelines[61].

E) Lifestyle Modification for PRP Optimization

E1) Smoking Cessation

Tobacco smoking compromises regenerative capacity through multiple mechanisms that negatively affect both PRP quality and target tissue responsiveness. It causes endothelial dysfunction, increases systemic inflammation, produces oxidative stress and affects fibroblast and chondrocyte function directly and these factors also interfere with tissue regeneration and make it less dependent on the quality of PRP.

Smoking also has a direct effect on platelet biology. The activation of platelets and aggregation ability is increased in smokers, and different growth factors expression profile can be turned into difficultly comparing to non-smokers. Smoking exposes tissues to carbon monoxide, which decreases oxygen reaching the tissue and impairs aerobic metabolism necessary for wound healing. Nicotine inhibits chondrocyte proliferation and matrix synthesis in the short term, but these effects continue even after PRP injection in the joint microenvironment[62].

Active smokers have much worse clinical outcomes after PRP. Smoking has emerged as a reproducible negative prognostic factor across studies involving musculoskeletal conditions treated with PRP, with smokers benefiting less in both magnitude and duration compared to non-smokers.

All candidates for PRP should therefore be counselled to quit smoking and treatment with PRP is best deferred until the patient has achieved abstinence. At least 4 weeks smoke-free leads to a significant

functional improvement of platelets and reduction of majority of inflammatory markers, with even better results after longer abstinence. Nicotine replacement therapy is also permissible during the cessation period, as they are less harmful than combusted tobacco; however, it would be preferable to discontinue all nicotine products prior to the initiation of PRP therapy as well[63].

E2) Alcohol Consumption

The clinical effect of alcohol on platelet function, inflammatory status and tissue healing is dose dependent. Light to moderate drinking tends to have a neutral or perhaps sometimes even beneficial effect on inflammatory markers, whereas heavy drinking promotes systemic inflammation, reduces liver synthetic capacity and directly inhibits regenerative processes. Chronic excessive alcohol consumption is linked with macrocytic anaemia, thrombocytopenia, and platelet dysfunction, all three of which may impair the quality of PRP[64].

The practice of acute alcohol use just prior to blood sampling for PRP preparation must be avoided. PRP may indeed be affected by alcohol consumption within 48 hours prior to testing or treatment as it changes platelet function. Patients who are heavy or troublesome alcohol users, at the time of pre-treatment optimization, need to receive counselling and support for reducing or ceasing use[65].

Practical recommendations are to refrain from alcohol for 48 hours prior to PRP blood collection, and preferably for 1 week (where baseline consumption is excessive). Patients may also be counselled to avoid any alcohol consumption for 2 weeks following PRP injection in order to optimize healing.

E3) Sleep Quality and Duration

Sleep is critical for the repair of tissues, effective immune function and the regulation of systemic inflammation. Sleep deprivation and decreased sleep quality are linked to increased inflammatory markers, reduced ability of the body to secrete growth hormone, and lesser healing response. Obstructive sleep apnea and insomnia are chronic sleep disorders inducing a proinflammatory milieu that might lead to reduced PRP efficacy[66].

Obstructive sleep apnea (OSA) deserves specific attention due to its very high prevalence among overweight and obese patients, who are often the main group of PRP candidates presented. OSA causes periodic hypoxemia, oxidative stress and inflammation even while overall night-time oxygen saturation is normal during wakefulness[67]. Continuous positive airway pressure (CPAP) treatment of OSA ameliorates inflammatory markers and may upregulate regenerative potential.

Pre-PRP evaluation, the patient should be screened for sleep disorders prior to PRP, which can and should use validated tools formalized by our previous protocols. Positive research workers should be made Bud or treated before the PRP therapy. All patients should be encouraged to optimize sleep hygiene in practice, targeting a sleep duration of 7 to 9 hours nightly[68].

E4) Physical Activity and Exercise

Physical activity has anti-inflammatory effects and benefits the metabolic syndrome, with possible direct actions on platelet function. Exercise training has been shown to decrease circulating inflammatory markers, increase insulin sensitivity and promote favourable body composition that all may support the efficacy of PRP. Proper exercise before and after PRP therapy may also maximize the mechanical conditions for tissue healing[69].

Nevertheless, careful consideration is needed of the timing and intensity of exercise in relation to PRP therapy. Intense exercise immediately before blood sampling can temporarily change platelet parameters[70]. Engaging in vigorous or impact-loading exercise post-PRP injection may impede healing. In contrast, prolonged immobility is not useful and even harms the outcome.

Recommendations of modest physical activity should be maintained throughout the pre-treatment optimization period, followed by a temporary reduction in exercise intensity for 24-48 hours prior to PRP blood collection in order to reduce platelet parameters. A progressive activity protocol should be implemented after PRP injection, starting with relative rest (24 to 72 hours), then range of-motion activities, and advancing into strengthening exercises

and functional activities over the next 4 to 6 weeks. Specific rehabilitation protocols must be tailored according to individual factors based on joint treated and patients[71].

E5) Hydration Status

Staying hydrated plays a very important role here for the viscosity of blood, better platelet function, and also successful sampling during blood draw required to prepare PRP. Dehydration increases blood components but may limit platelet activity and make the process of blood collection more difficult. Patients should be advised to keep hydrated in the days before PRP therapy, being mindful of an adequate fluid intake (approximately 2 to 3 liters/day) on the day prior and morning of the procedure[72,73].

F) Systemic Diseases Optimisation

F1 ) Autoimmune and Inflammatory Conditions

PRP therapy poses special problems among patients with rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus or similar autoimmune disorders. These conditions provide a systemic inflammatory environment that can supersaturate the local anti-inflammatory effects of PRP. Moreover, immunomodulatory drugs that are often used in these diseases may influence the composition of PRP or the responsiveness of target tissues[74].

When an underlying autoimmune condition is present, disease activity should be optimized prior to PRP therapy. Disease-modifying antirheumatic drugs (DMARDs) need to continue to control the disease where flaring autoimmune activity would simply be more damaging in terms of PRP outcomes than avoiding medication. Most biologic agents that do not directly inhibit platelet function (TNF inhibitors, IL-6 inhibitors, B-cell depleting agents) can be continued. Nevertheless, when utilizing PRP in conjunction with biologics for treatment of AS, one should also consider the timing of each intervention; delivery of PRP at specified nadir of biologic dosing (for example: 4 hours prior to next scheduled dose) may be preferable[75,76].

F2) Chronic Kidney Disease

Platelet dysfunction due to accumulation of uremic toxins is responsible for the bleeding diathesis seen in advanced chronic kidney disease (CKD). Uremic patients exhibit reduced platelet aggregation and adhesion. Moreover, damaged regenerative capacity is compounded due of chronic inflammation, oxidative stress and Vitamin D deficiency associated with CKD[77].

Optimization of renal patients[78,79] :

- Adequate dialysis in end stage kidney disease
- Anemia correction (target Hb 10–11 g/dL)
- Vitamin D deficiency correction. In patients with CKD stages 3-4, optimization of BP, glycaemic control (if diabetic) and cardiovascular risk factors favors renal preservation and PRP outcome.

F3) Hematologic Considerations

PRP quality is obviously dependent on baseline platelet count and function. Any source of thrombocytopenia creates an inability to produce concentrated PRP. When the sample is not activated, conditions associated with platelet dysfunction (myeloproliferative disorders, inherited platelet disorders, acquired platelet dysfunction due to medications or uremia) may result in PRP with impaired activating potential[80].

Complete blood count before treatment should be done in all PRP candidates. Thrombocytopenia was defined as a platelet count 150,000/iL and requires proper evaluation for the etiology. Platelet counts greater than 200 000/iL are ideal for preparing PRP. Patients with documented platelet dysfunctions should be treated accordingly, as cases of severe inherited platelet disorders can reflect a relative contraindication to PRP therapy[81,82].

G) Psychological Preparation and Expectations

G1) Educating Patients & Expectations

Clinical outcomes reported by patients following any intervention, including PRP therapy, are significantly influenced by psychological factors. Unrealistic expectations (overly optimistic/pessimistic) are related to both subjective and potentially objective outcomes through psychobiological pathophysiological mechanisms. Proper education of patients sets realistic expectations and potentially increases both placebo responses and biological activity[83].

Pre-treatment education should include the mechanism of PRP therapy, anticipated onset time course (usually 4–8 weeks to appreciate initial improvement, continuing gains over 3-6 months), realistic magnitude of gain (usually e 50–70% reduction in pain but rarely complete resolution of symptoms) and encourage patience and adherence to post-procedural rehabilitation. Patients must realize that PRP is a healer but does not reverse extensive structural damage[84].

G2) Psychological Distress and Chronic Pain Psychology

Depressive symptoms, anxiety and catastrophizing have their presence in populations with chronic pain and have a potential negative influence on outcomes across various treatment approaches. These psychological factors affect the perception of pain, willingness to seek medical treatment, and physiological stress responses that could impede healing. Optimizing psychological comorbidity before PRP therapy may optimize outcomes and psychosocial functioning.

It's essential to include screening for depression and anxiety in pre-treatment assessment using standardized tools like the Patient Health Survey-9 (PHQ-9) or Generalized Anxiety Disorder-7 (GAD-7). Patients who screen too positively should be referred for appropriate psychological help before or during PRP therapy. Particularly relevant may be cognitive behavioural therapy modalities that are geared toward the reduction in catastrophizing of pain.

G3) Treatment Engagement and Self-Efficacy

The course of treatment, which includes not only pre-treatment optimization protocols and post-procedural rehabilitation that patients are encouraged to follow, has a direct effect on outcomes[85]. Self-efficacy, the belief that they can change their own outcomes, predicts treatment success in diverse scenarios.

Methods to increase adherence include involvement of the patient in goal setting, written instructions for pre- and post-treatment protocols and follow-up scheduling, with an emphasis on reinforcement. Motivational interviewing techniques can be helpful for the patient who is uncertain regarding lifestyle changes, which are key to his success[86].

H) Others

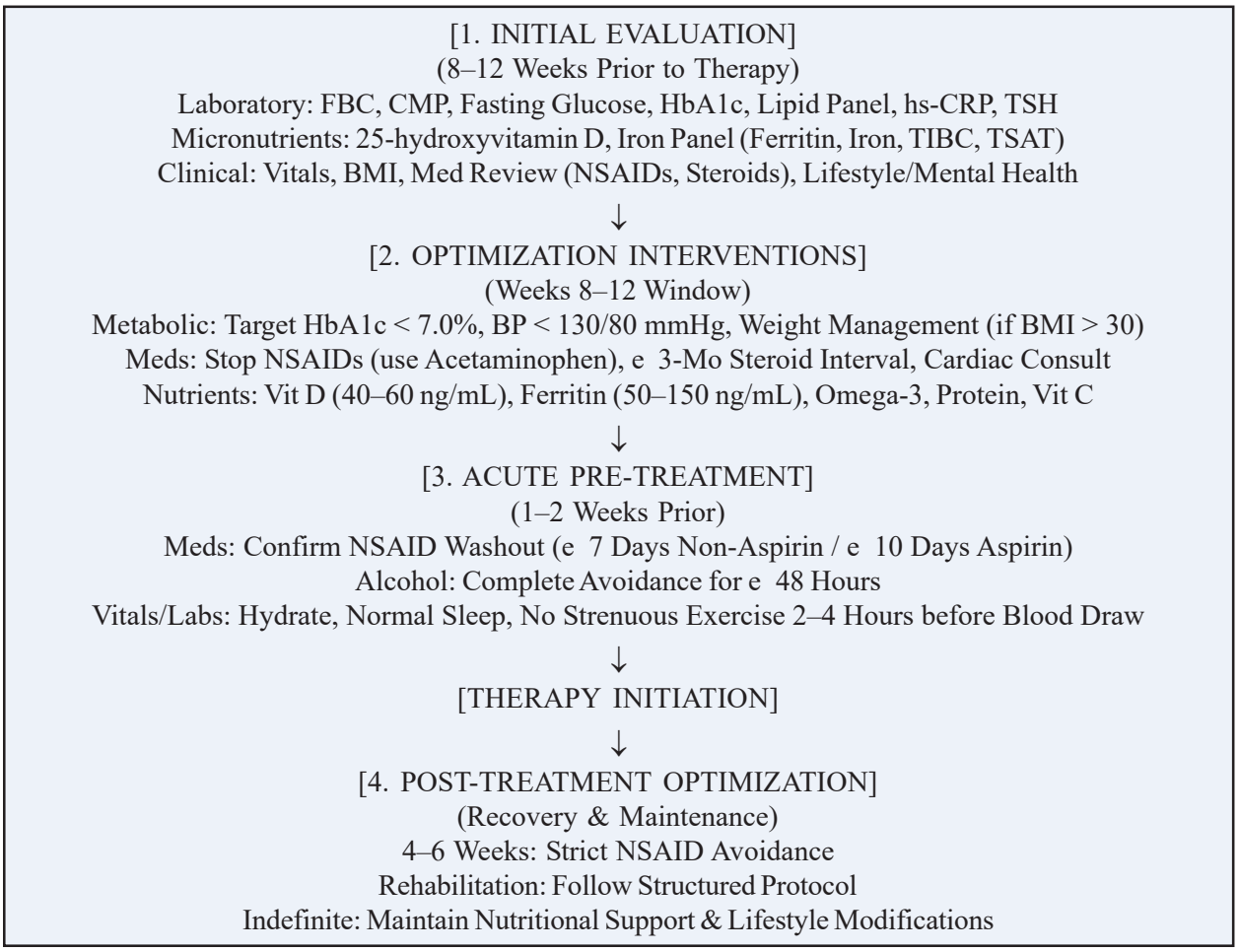
H1) Athletes and Other Highly Physically Active Persons

Athletes represent unique challenges because of the need for rapid return to sport, high mechanical load through healing tissues and in many cases excessive motivation in relation to optimization protocols. Significance of loading model- The rehabilitation protocol after surgery must consider a balance between the amount of loading to be applied on the tissue and excessive stress in recovery among others[87].

This review suggests that optimizations prior to treatment in athletes should be aimed at: (1) training load; (2) nutrition, particularly energy availability and protein intake; and (3) psychology preparedness during period of reduced activity during treatment[88]. Sport-specific rehabilitative protocols should then ideally be refined in collaboration with the relevant sports medicine and rehabilitation staff.

H2) Patients with Multiple Previous Failed Lines of Therapy

A detailed analysis of the causes for past failure is crucial was it due to insufficient PRP preparation, insufficient patient optimization, or wrong treatment technique. In some patients, the severity or biology of the disease is such that response to any available regenerative strategy will be limited[89]. Among factors that were never intended to target, all should be optimally controlled in patients with prior PRP failure. However, alternative protocols for PRP preparation (leukocyte-rich versus poor, varying platelet concentration or activation methods) may be warranted. Combined approaches (i.e PRP plus bone marrow aspirate concentrate or that isolated from adipose tissue) may be another consideration for certain patients[90]. To have realistic expectations the chance of success being very low.




An algorithmic approach to patient optimization prior PRP therapy

## Future Directions and Research Priorities

Although patient optimization appears to be an important component of cancer care, the evidence is sparse and many critical knowledge gaps remain. The ability to demonstrate definitive clinical benefit from these protocols would require controlled prospective studies comparing outcomes in optimized versus non-optimized patients. Identification of predictive biomarkers predicting who is likely to benefit from PRP & those who may respond better after optimization will pave the way towards precision medicine.

Real-time treatment decisions should be possible through the point-of-care tests developed to quantitatively measure PRP quality and to evaluate patient specific variables in terms of their regenerative potential. A further important avenue of future research relates to adjunctive therapies that could potentiate results in challenging patients. Finally, health economic analyses of optimization protocols should specifically be based on task-based outcomes in order to inform their implementation in resource-limited healthcare settings.

## Conclusions:

The concept of patient optimization complements a paradigm shift in regenerative medicine thinking from viewing protocol driven PRP as an indiscriminate treatment to appreciating it as a targeted biologic therapy, which generates therapeutic action only in the context of patient factors that are independent of any intervention procedures All this evidence summarized in this article indicates that, depending on the environment (metabolic health and nutritional status), medication exposure, lifestyle factors, comorbidity situations and psychological states, quality of PRP prepared and clinical healing response varies. One rational strategy for improving outcomes would be to modulate such factors through evidence-based

approaches in the weeks before PRP therapy, with a structured pathway focused on optimizing the patient. The biological plausibility and small risk of optimization protocols favour their application into clinical practice until definitive trials have occurred. Clinical practice guidelines should incorporate standardized pre-treatment protocols.

## Declaration:

Ethics approval: The study was approved by the Ethical Review Board.

**Author contributions**

Conception and development of the idea: SD, MC, LS
Writing: SD, MC, LS
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