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O caminho não trilhado (De Robert Frost)

Dois caminhos divergiam em um bosque amarelo
E pena foi não pode seguir por ambos,
Sendo apenas um viajante, por longo tempo fiquei
E olhei um deles o mais longe que pude
Até onde a curva da vegetação o escondia.

Então segui pelo outro, igualmente belo,
E tendo, talvez, melhor razão,
Pois era gramado e pedia para ser trilhado;
Porém, passando no caminho, percebi que
Eram trilhados quase da mesma forma.

E ambos naquela manhã igualmente jaziam
Com folhas, que nenhum passo tinha pisado.
Oh, eu deixei o primeiro para outro dia!
Já sabendo que um caminho leva a outro,
Duvidei que algum dia eu pudesse voltar.

Hei de contar isto com um suspiro
Em algum lugar num futuro distante:
Dois caminhos divergiam em um bosque, e eu –
Eu segui pelo menos trilhado,
E isto fez toda a diferença.

Aos mestres e amigos que nos apresentaram e incentivaram a trilhar o caminho SEM volta da Medicina Regenerativa: *Joseph Purita, Philippe Hernigou, Ramón Cugat e Peter Everts.*

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Produções Científicas

2013 a 2019

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ARTIGO

Prediction and Modulation of Platelet Recovery by Discontinuous Centrifugation of Whole Blood for the Preparation of Pure Platelet-Rich Plasma

- Amanda G.M. Perez
- Rafael Lichy
- **José Fábio S.D. Lana**
- Ana Amélia Rodrigues
- Ângela Cristina M. Luzo
- William D. Belangero
- Maria Helena A. Santana

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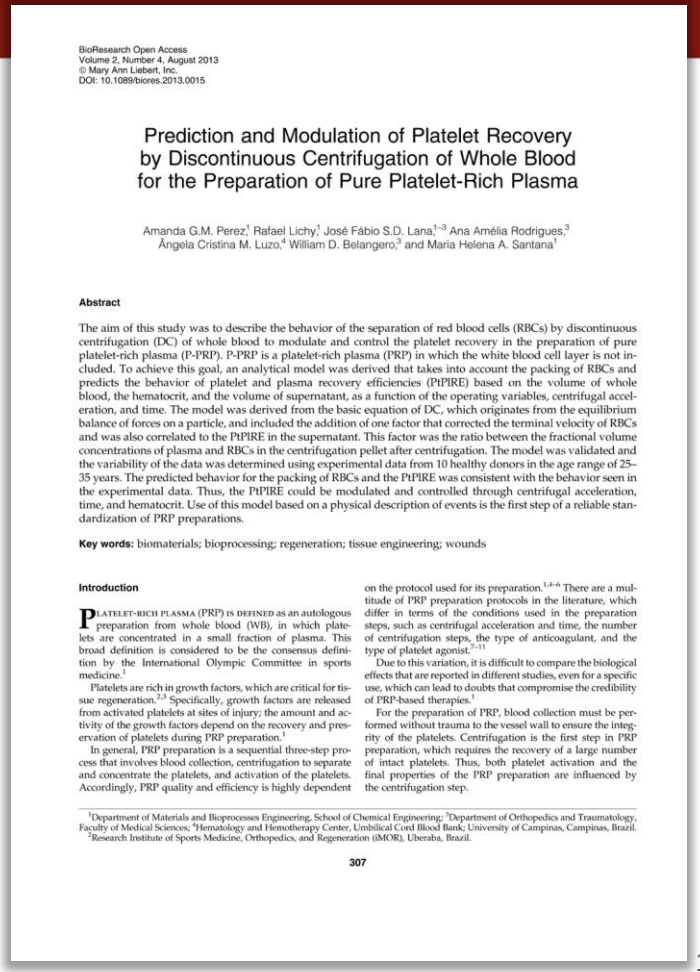

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Prediction and Modulation of Platelet Recovery by Discontinuous Centrifugation of Whole Blood for the Preparation of Pure Platelet-Rich Plasma

Amanda G.M. Perez,[1] Rafael Lichy,[1] José Fábio S.D. Lana,[1–3] Ana Amélia Rodrigues,[3] Ângela Cristina M. Luzo,[4] William D. Belangero,[3] and Maria Helena A. Santana[1]

Abstract

The aim of this study was to describe the behavior of the separation of red blood cells (RBCs) by discontinuous centrifugation (DC) of whole blood to modulate and control the platelet recovery in the preparation of pure platelet-rich plasma (P-PRP). P-PRP is a platelet-rich plasma (PRP) in which the white blood cell layer is not included. To achieve this goal, an analytical model was derived that takes into account the packing of RBCs and predicts the behavior of platelet and plasma recovery efficiencies (PtPIRE) based on the volume of whole blood, the hematocrit, and the volume of supernatant, as a function of the operating variables, centrifugal acceleration, and time. The model was derived from the basic equation of DC, which originates from the equilibrium balance of forces on a particle, and included the addition of one factor that corrected the terminal velocity of RBCs and was also correlated to the PtPIRE in the supernatant. This factor was the ratio between the fractional volume concentrations of plasma and RBCs in the centrifugation pellet after centrifugation. The model was validated and the variability of the data was determined using experimental data from 10 healthy donors in the age range of 25–35 years. The predicted behavior for the packing of RBCs and the PtPIRE was consistent with the behavior seen in the experimental data. Thus, the PtPIRE could be modulated and controlled through centrifugal acceleration, time, and hematocrit. Use of this model based on a physical description of events is the first step of a reliable standardization of PRP preparations.

Key words: biomaterials; bioprocessing; regeneration; tissue engineering; wounds

Introduction

PLATELET-RICH PLASMA (PRP) IS DEFINED as an autologous preparation from whole blood (WB), in which platelets are concentrated in a small fraction of plasma. This broad definition is considered to be the consensus definition by the International Olympic Committee in sports medicine.[1]

Platelets are rich in growth factors, which are critical for tissue regeneration.[2,3] Specifically, growth factors are released from activated platelets at sites of injury; the amount and activity of the growth factors depend on the recovery and preservation of platelets during PRP preparation.[1]

In general, PRP preparation is a sequential three-step process that involves blood collection, centrifugation to separate and concentrate the platelets, and activation of the platelets. Accordingly, PRP quality and efficiency is highly dependent on the protocol used for its preparation.[1,4–6] There are a multitude of PRP preparation protocols in the literature, which differ in terms of the conditions used in the preparation steps, such as centrifugal acceleration and time, the number of centrifugation steps, the type of anticoagulant, and the type of platelet agonist.[7–11]

Due to this variation, it is difficult to compare the biological effects that are reported in different studies, even for a specific use, which can lead to doubts that compromise the credibility of PRP-based therapies.[1]

For the preparation of PRP, blood collection must be performed without trauma to the vessel wall to ensure the integrity of the platelets. Centrifugation is the first step in PRP preparation, which requires the recovery of a large number of intact platelets. Thus, both platelet activation and the final properties of the PRP preparation are influenced by the centrifugation step.

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ARTIGO

Relevant Aspects of Centrifugation Step in the Preparation of Platelet-Rich Plasma

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- Ana Amélia Rodrigues
- Ângela Cristina M. Luzo
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Research Article

Relevant Aspects of Centrifugation Step in the Preparation of Platelet-Rich Plasma

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Introduction. Platelet-Rich Plasma (PRP) is rich in growth factors, playing important role in tissue healing. The wide variation of reported protocols for preparation of PRP leads to variable compositions, which induce different biological responses and prevent results comparison. This study aims to highlight relevant aspects of the centrifugation step to obtain reproducible results and overall quality. *Material and Methods.* Samples of blood were collected from 20 healthy donors that have signed free informed consent. Two centrifugation steps (spins) were analyzed for the influence of centrifugal acceleration, time, processed volume, and platelet gradient. The Pure Platelet-Rich Plasma (P-PRP) was characterized as platelet concentration, integrity, and viability (sP-selectin measurement). *Results.* Lower centrifugal accelerations favour platelet separation. The processing of 3.5 mL of blood at 100 ×g for 10 min (1st spin), 400 ×g for 10 min (2nd spin), withdrawing 2/3 of remnant plasma, promoted high platelet recovery (70–80%) and concentration (5x) maintaining platelet integrity and viability. The recovery of platelets was reduced for a larger WB volume (8.5 mL) processed. *Conclusion.* Centrifugal acceleration, time, WB processed volume, and minimization of the platelet gradient before sampling are relevant aspects to ensure reproducible compositions within the autologous nature of PRP.

1. Introduction

Platelet-Rich Plasma (PRP) is an autologous preparation that concentrates platelets in a small volume of plasma [1]. Platelets are rich in growth factors, which play an important role in tissue healing. Numerous studies have demonstrated the clinical application and notable results of PRP in dentistry [2], oral maxilla facial surgery [3], plastic surgery [4], orthopedics [5], rheumatology [6], and the treatment of different types of injuries that include chronic wounds [7, 8] and muscle injuries [9].

PRP is made for two purposes: one for harvesting platelets for therapeutic purposes and the other for testing for platelet function in PRP using aggregometry. In this work it was studied for therapeutic purposes only.

The wide variation in the reported protocols for obtaining PRP may lead to samples with different compositions that may induce different biological responses [1]. Despite these variations, all protocols follow a generic sequence that consists of blood collection, an initial centrifugation to separate red blood cells (RBC), subsequent centrifugations to concentrate platelets, and other components and an activation of the sample by adding a platelet agonist (Figure 1). Prior to the platelet activation step, variables in the process that may influence the platelet integrity along with the composition and effectiveness of the PRP include the number of spins, centrifugal acceleration, and time period of centrifugation [10]. In addition to the platelets, the white blood cells (WBC) composition may also be analyzed, as the concentration of these cells is also an important factor in tissue healing [11].

ARTIGO

Fibrin network architectures in pure platelet-rich plasma as characterized by fiber radius and correlated with clotting time

- Amanda G. M. Perez
- Ana A. Rodrigues
- Ângela C. M. Luzo
- **José F. S. D. Lana**
- William D. Belangero
- Maria H. A. Santana

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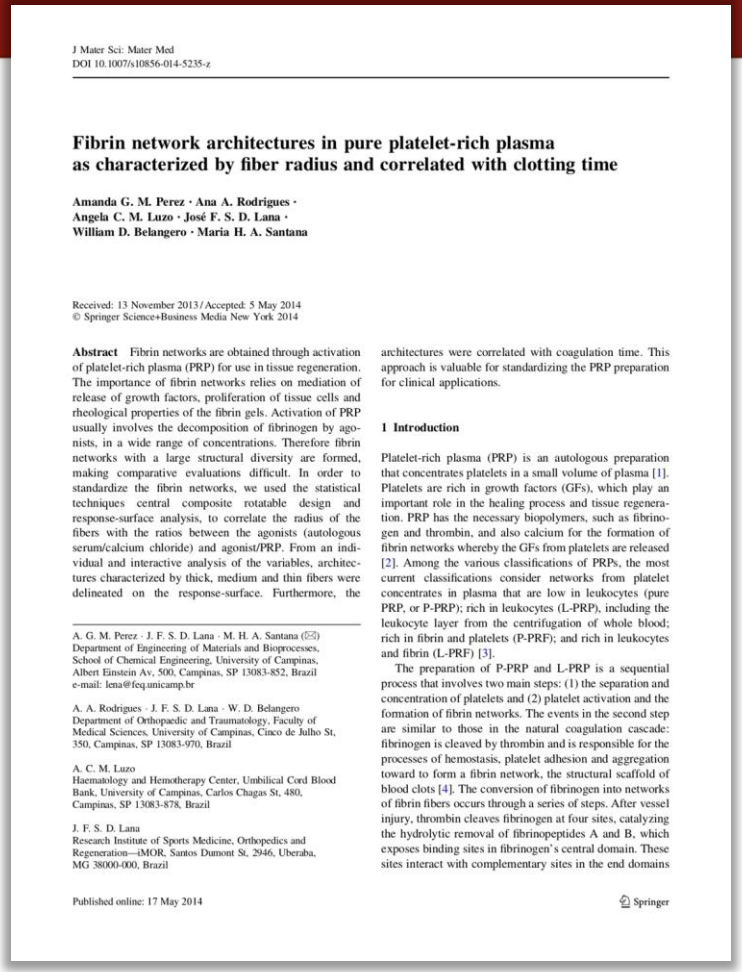

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Fibrin network architectures in pure platelet-rich plasma as characterized by fiber radius and correlated with clotting time

Amanda G. M. Perez · Ana A. Rodrigues · Angela C. M. Luzo · José F. S. D. Lana · William D. Belangero · Maria H. A. Santana

Received: 13 November 2013 / Accepted: 5 May 2014

Abstract Fibrin networks are obtained through activation of platelet-rich plasma (PRP) for use in tissue regeneration. The importance of fibrin networks relies on mediation of release of growth factors, proliferation of tissue cells and rheological properties of the fibrin gels. Activation of PRP usually involves the decomposition of fibrinogen by agonists, in a wide range of concentrations. Therefore fibrin networks with a large structural diversity are formed, making comparative evaluations difficult. In order to standardize the fibrin networks, we used the statistical techniques central composite rotatable design and response-surface analysis, to correlate the radius of the fibers with the ratios between the agonists (autologous serum/calcium chloride) and agonist/PRP. From an individual and interactive analysis of the variables, architectures characterized by thick, medium and thin fibers were delineated on the response-surface. Furthermore, the architectures were correlated with coagulation time. This approach is valuable for standardizing the PRP preparation for clinical applications.

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1 Introduction

Platelet-rich plasma (PRP) is an autologous preparation that concentrates platelets in a small volume of plasma [1]. Platelets are rich in growth factors (GFs), which play an important role in the healing process and tissue regeneration. PRP has the necessary biopolymers, such as fibrinogen and thrombin, and also calcium for the formation of fibrin networks whereby the GFs from platelets are released [2]. Among the various classifications of PRPs, the most current classifications consider networks from platelet concentrates in plasma that are low in leukocytes (pure PRP, or P-PRP); rich in leukocytes (L-PRP), including the leukocyte layer from the centrifugation of whole blood; rich in fibrin and platelets (P-PRF); and rich in leukocytes and fibrin (L-PRF) [3].

The preparation of P-PRP and L-PRP is a sequential process that involves two main steps: (1) the separation and concentration of platelets and (2) platelet activation and the formation of fibrin networks. The events in the second step are similar to those in the natural coagulation cascade: fibrinogen is cleaved by thrombin and is responsible for the processes of hemostasis, platelet adhesion and aggregation toward to form a fibrin network, the structural scaffold of blood clots [4]. The conversion of fibrinogen into networks of fibrin fibers occurs through a series of steps. After vessel injury, thrombin cleaves fibrinogen at four sites, catalyzing the hydrolytic removal of fibrinopeptides A and B, which exposes binding sites in fibrinogen's central domain. These sites interact with complementary sites in the end domains

ARTIGO

In vitro study of the role of thrombin in platelet rich plasma (PRP) preparation: utility for gel formation and impact in growth factors release

- Stephany Cares Huber
- José Luiz Rosenberis Cunha Júnior
- Silmara Montalvão
- Letícia Queiroz da Silva
- Aline Urban Paffaro Francesca
- Aparecida Ramos da Silva
- Bruno Lima Rodrigues
- **José Fabio Santos Duarte Lana**
- Joyce Maria Annichinno-Bizzacchi

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RESEARCH ARTICLE

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In vitro study of the role of thrombin in platelet rich plasma (PRP) preparation: utility for gel formation and impact in growth factors release

Huber SC[1], Cunha JL[1], Montalvão SAL[1], da Silva LQ[1], Paffaro AU[1], da Silva FAR[1], Rodrigues BL[1], Lana JFSD[1], Annichino-Bizzacchi JM[1]

Introduction: The use of PRP has been studied for different fields, with promising results in regenerative medicine. Until now, there is no study in the literature evaluating thrombin levels in serum, used as autologous thrombin preparation. Therefore, in the present study we evaluated the role played by different thrombin concentrations in PRP and the impact in the release of growth factors. Also, different activators for PRP gel formation were evaluated. **Methods:** Thrombin levels were measured in different autologous preparations: serum, L-PRP (PRP rich in leukocytes) and T-PRP (thrombin produced through PRP added calcium gluconate). L-PRP was prepared according to the literature, with platelets and leukocytes being quantified. The effect of autologous thrombin associated or not with calcium in PRP gel was determined by measuring the time of gel formation. The relationship between thrombin concentration and release of growth factors was determined by growth factors (PDGF-AA, VEGF and EGF) multiplex analysis. **Results:** A similar concentration of thrombin was observed in serum, L-PRP and T-PRP (8.13 nM, 8.63 nM and 7.56 nM, respectively) with a high variation between individuals (CV%: 35.07, 43 and 58.42, respectively). T-PRP and serum with calcium chloride showed similar results in time to promote gel formation. The increase of thrombin concentrations (2.66, 8 and 24 nM) did not promote an increase in growth factor release. **Conclusions:** The technique of using serum as a thrombin source proved to be the most efficient and reproducible for promoting PRP gel formation, with some advantages when compared to other activation methods, as this technique is easier and quicker with no need of consuming part of PRP. Noteworthy, PRP activation using different thrombin concentrations did not promote a higher release of growth factors, appearing not to be necessary when PRP is used as a suspension.

Key Words: Platelet Rich Plasma, Thrombin, gel, Leukocytes, Growth factor

Introduction

Platelet rich plasma (PRP) is defined as a concentrate preparation that increases between 4 to 9 folds the basal number of platelets, in reduced plasma volume[1]. Platelets contain over 1100 proteins including growth factors, messengers of the immune system, enzymes, enzyme inhibitors and other bioactive compounds. These factors can improve tissue repair by diverse mechanisms including regulation of inflammation, angiogenesis, synthesis and remodeling of new tissues[2, 3]. For these reasons, PRP has been used in different fields: odontology[4], plastic surgery[5], orthopedics[6], wound healing[7] and aesthetics[8] with promising results. However, biomolecules are known to be quickly released from PRP, losing their activity in a short period of time which could represent a challenge in clinical practice[9].

PRP preparations have been used since 1970s, however they become popular in 1990s. Since then, different protocols emerged to prepare PRP including commercial systems[10]. Despite the promising results published by different research groups, the heterogeneity of protocols for PRP preparation available, render the evaluation of a consistent therapeutic effect quite difficult. *In vitro* studies evidenced that the different methodologies used in the preparation of PRP can affect biological aspects and clinical effects, which depend on several variables, particularly platelet and growth factor concentration, presence or absence of leukocytes and the type of activation[2].

PRP is usually prepared by double centrifugation of anticoagulated blood. The first spin is to separate red blood cells and plasma; the second spin is to concentrate platelets. Despite the existing PRP standardization proposals, there is no consensus regarding centrifugation force or duration. This absence of a standard PRP preparation inhibits any comparisons of treatment efficacy obtained by different research groups. The inclusion or not of leukocytes is also widely discussed in the literature. PRP with leukocytes (L-PRP) presents different biologic activity, which could modify the therapeutic effect[11].

Another important issue is the activation for growth factor release. This activation can be induced by bovine or autologous thrombin, calcium chloride, collagen, freeze & thaw cycles and mechanical trauma. Collagen and thrombin activate platelets by different mechanisms. For the activation of platelets by collagen, they must first adhere to collagen and then became active by it through a second receptor. This kind of platelet activation may require a lengthier mechanism than the cleavage process of thrombin-mediated platelet activation[12]. Park and collaborators demonstrated that thrombin is a strong agonist for induction of PRP cytokines and growth factors release when compared to ADP + calcium or collagen[13]. Once PRP activation is achieved, a fibrin network begins to form with a rapid growth factor release during the first hour, continuing to release cytokines and growth factors from their mRNA for at least another 7 days[14, 15].

Author Names in full: Stephany Cares Huber[1], José Luiz Rosenberis Cunha Júnior[1], Silmara Montalvão[1], Letícia Queiroz da Silva[1], Aline Urban Paffaro[1], Francesca Aparecida Ramos da Silva[1], Bruno Lima Rodrigues[1], José Fabio Santos Duarte Lana[1], Joyce Maria Annichinno-Bizzacchi[1]

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ARTIGO

Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee

- José F. S. D. Lana
- Adam Weglein
- Steve E. Sampson
- Eduardo F. Vicente
- Stephany Cares Huber
- Clarissa V. Souza
- Mary A. Ambach Hunter
- Vincent Aline Urban-Paffaro
- Carolina M. K. Onodera
- Joyce M. Annichino-Bizzacchi
- Maria Helena A. Santana
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RESEARCH ARTICLE

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Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee

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Objective: This study aims at evaluating the clinical effects of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) as individual treatments for mild to moderate Osteoarthritis (OA) and it also examines the potential synergistic effects of PRP in combination with HA. Research continues to emerge examining the potential therapeutic efficacy of HA and PRP as autologous injectable treatments for joint arthritis. However, there is a paucity of research investigating the effects of combining HA and PRP on pain and functional status in patients withOA.
Design: In this multi-center, randomized, controlled, double blind, prospective trial, 105 patients with mild to moderate knee osteoarthritis, who met the study criteria, were randomly allocated to one of three interventions: HA (n=36), PRP (n=36), or HA+PRP (n=33). Each patient received 3 intra-articular knee injections of their assigned substance, with 2 week intervals between each injection. Clinical outcomes were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale (VAS) questionnaire at baseline and after 1,3,6 and 12 months.
Results: The study showed that the PRP group have significant reduction in VAS scores at 1 (p= 0.003), 3 (p= 0.0001), 6 (p= 0.0001) and 12 (p= 0.000) months when compared to HA. In addition, the PRP group illustrated greater improvement in WOMAC physical activity scale at 12 months (p= 0.008) when compared to the HA group. Combining HA and PRP resulted in a significant decreases in pain (p=0.0001) and functional limitation (p=0.0001) when compared to HA alone at 1 year post treatment; and significantly increased physical function at 1 (p=0.0004) and 3 (p=.011) months when compared to PRP alone.
Conclusion: The findings of the study support the use of autologous PRP as an effective treatment of mild to moderate knee osteoarthritis. It also shows that the combination of HA and PRP resulted to better outcomes than HA alone up to 1 year and PRP alone up to 3 months. Furthermore, the results suggest that combination of PRP and HA could potentially provide better functional outcomes in the first 30 days after treatment with both PRP and HA alone.

Key Words: Hyaluronic acid, Joint pathology, Knee, Osteoarthritis, Platelet-rich plasma

Introduction

Osteoarthritis of the knee joint has a great impact on physical performance and is considered one of the ten major causes of disability in the world. Standard conservative treatments for knee osteoarthritis include: weight loss, physical exercises, use of non-steroid anti-inflammatory agents, analgesics, injection of hyaluronic acid (HA) and injection of glucocorticoids[1,2]. Although, standard conservative measures can provide symptomatic improvements, they are not without their limitations. Steroid injections are common practice among practitioners, including orthopedic surgeons, however, prolonged use of such pharmacological treatments may have adverse effects on existing cartilage[3]. Also, chronic use of anti- inflammatory medications may cause nephrotoxicity and gastrointestinal side effects[3]. However, recently, Orthobiologic injections have emerged as a potentially safe and efficacious option for joint Osteoarthritis.

Hyaluronic Acid (HA) is currently a widely used injectable treatment for degenerative joint pathology. It is a glycosaminoglycan that acts as a backbone for proteoglycans of the extracellular matrix[4], providing increased joint lubrication. Studies have demonstrated that HA has positive therapeutic efficacy for knee osteoarthritis with initial efficacy at 4 weeks, and peak effectiveness at 8 weeks which lasts for up to 6 months[5]. When compared to continuous oral NSAIDS or other anti-inflammatory medications, HA has illustrated comparable, if not greater, therapeutic effects on knee OA with a better safety profile[5,6].

Autologous platelet rich plasma (PRP) has also emerged as an alternative in the context of injectable treatment for OA. PRP is comprised of a potent cellular milieu containing platelet concentrations above baseline, as well as an undifferentiated mixture of anti-inflammatory, pro-inflammatory, anabolic and catabolic mediators in an attempt to stimulate a supra-physiologic response and elicit the body's natural healing potential. Currently, most studies on PRP are anecdotal or case reports with small sample sizes. However, larger randomized controlled trials have demonstrated superior efficacy in areas such as tendinopathies[7] and knee osteoarthritis[8].

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ARTIGO

The use of platelet rich plasma in the treatment of refractory Crohn's disease

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- Bruno Lima Rodrigues
- Stephany Cares Huber
- Jose Luiz Rosenberis Cunha Júnior
- **José Fábio Santos Duarte Lana**
- Silmara Aparecida de Lima Montalvã
- Ângela Cristina Malheiros Luzo
- Maria Lourdes Setsuko Ayrizono
- Cláudio Saddy Rodrigues Coy
- Raquel Franco Leal
- Joyce Maria Annichino-Bizzacchi

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Original Article

The use of platelet rich plasma in the treatment of refractory Crohn's disease

Francesca Aparecida Ramos da Silva[1], Bruno Lima Rodrigues[1], Stephany Cares Huber[1], Jose Luiz Rosenberis Cunha Júnior[1], José Fabio Santos Duarte Lana[1], Silmara Aparecida de Lima Montalvão[1], Ângela Cristina Malheiros Luzo[1], Maria Lourdes Setsuko Ayrizono[2], Cláudio Saddy Rodrigues Coy[2], Raquel Franco Leal[2*], Joyce Maria Annichino-Bizzacchi[1*]

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Abstract: Crohn's disease (CD) is a complex and multifactorial pathology. About 40% of patients cease to respond after available clinical therapy. Platelet rich plasma (PRP) is an alternative therapy widely used in the orthopedics and dentistry fields. Most recently, it has been studied in dermatological affections and autoimmune diseases. The aim was to evaluate the role of Platelet rich plasma (PRP) for refractory CD patients. Five patients diagnosed with ileocolic CD were selected. These patients were not taking any medication for at least two months and were resistant to biological therapy for at least one year. Growth factors, C-reactive protein, platelet and regulatory T cell frequency were measured at two different times: before treatment and after 12 injections of PRP (once a week). The activity of the disease was based on clinical and endoscopic indexes. The endoscopic score after PRP decreased in comparison to the baseline in four patients. Four patients had clinical remission, including the absence of joint pain. Two patients with perianal CD showed a decrease of discharge. No adverse effects such as allergic reactions were observed. Our findings suggest a short-term benefit of PRP for most refractory CD patients in this case series.

Keywords: Platelet rich plasma, Crohn's disease, inflammatory bowel disease

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease with unknown etiology, and it may affect any part of the gastrointestinal tract, especially the terminal ileum. CD is characterized by the formation of ulcers, fistulas and strictures, with periods of worsening and remission [1]. Immune factors are directly associated with CD: the patients present Th1/Th17 and Treg (regulatory T cell) disorders, which support the inflammatory symptoms [2]. The conventional clinical treatments comprise the use of immunosuppressive drugs and biological therapy. Besides the side effects, after a period of drug intake, 40% of the patients no longer respond to the treatment [3]. Therefore, the search for new effective treatments to induce a remission is needed.

Platelet-rich plasma (PRP) is a result of peripheral blood processing. It presents high concentration of platelet [4]. This concentration is up to five times higher than the baseline platelet count (about 1 million platelet per microliter) [4, 5]. Recent studies are evaluating the functions of platelets more broadly, beyond hemostatic functions. Platelets participate in the inflammation process by releasing substances able to modulate inflammatory response by cell interactions to endothelial cells and leukocytes. PDGF, TGF-β, CD40L and CD154 are found among the immunomodulatory factors [6]. TGF-β is the main immunosuppressive molecule that influences Treg differentiation. This became evident in a study of immune thrombocytopenia, characterized by a decrease of Treg and TGF-β that showed a functional and quantitative Treg restoration after being treated with therapies that increase the platelet count [7]. Due to the immunomodulatory characteristics, especially Treg differentiation by TGF-β, PRP has the potential of being a therapeutic option for refractory CD. The objective of this study

ARTIGO

Contributions for classification of platelet rich plasma – proposal of a new classification: MARSPILL

- José Fábio Santos Duarte Lana
- Joseph Purita
- Christian Paulus
- Stephany Cares Huber
- Bruno Lima Rodrigues
- Ana Amélia Rodrigues
- Maria Helena Santana
- João Lopo Madureira Jr.
- Ângela Cristina Malheiros Luzo
- William Dias Belangero
- Joyce Maria Annichino Bizzacchi

Publicação: 31 de Julho de 2017
Veículo: FSG - Future Medicine

Pesquisa completa aqui!

Special Report

Regenerative Medicine

Contributions for classification of platelet rich plasma – proposal of a new classification: MARSPILL

Platelet-rich plasma (PRP) has emerged as a significant therapy used in medical conditions with heterogeneous results. There are some important classifications to try to standardize the PRP procedure. The aim of this report is to describe PRP contents studying celular and molecular components, and also propose a new classification for PRP. The main focus is on mononuclear cells, which comprise progenitor cells and monocytes. In addition, there are important variables related to PRP application incorporated in this study, which are the harvest method, activation, red blood cells, number of spins, image guidance, leukocytes number and light activation. The other focus is the discussion about progenitor cells presence on peripherial blood which are interesting due to neovasculogenesis and proliferation. The function of monocytes (in tissue-macrophages) are discussed here and also its plasticity, a potential property for regenerative medicine treatments.

First draft submitted: 22 March 2017; Accepted for publication: 31 May 2017; Published online: 31 July 2017

Keywords: growth factors • leukocytes • mononuclear cells • platelet-rich plasma • regenerative medicine

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Platelet-rich plasma (PRP) can be considered as a form of autologous nonimmunogenic therapy, which contains a high concentration of growth factors (GFs) and cytokines. It plays important actions in various stages of regeneration and tissue repair [1,2].

According to the literature, PRP activation bursts the release of platelet α-granules, which are rich in proteins and GFs, such as PDGF, TGF-β, IGF, VEGF and EGF. All these molecules are important in different stages of tissue regeneration. They act as regulatory agents, stimulating chemotaxis and cellular differentiation and proliferation [2–5].

PRP has been widely investigated and used in medicine (orthopedics [6,7], dermatology [8] and plastic surgery), odontology [9] and veterinary medicine [10,11] due to its properties and simplicity to obtain the product. It is obtained with the use of commercial kits or not automated techniques (*in house*) that results in different types of PRP. Despite the increasing number of studies and some classifications published, there is no consensus regarding the classification used for different types of PRP. These procedures are obtained via machine or in house. As a consequence, different terminologies may be observed for the same type of PRP and vice-versa [12].

Given the numerous classifications presented, the purpose of this report is to describe the main types of PRP in the literature. And also, from the critical analysis of these publications, to propose a terminology based on the main parameters used during the preparation of PRP. Thus, some variables, such as automated method (machine) or not, spin cycles number, activation form, presence or absence of cells, fibrin and concentration of different factors and cytokines that compose PRP, must not only be well defined, but also be easily identified.

10.2217/rme-2017-0042 © 2017 Jose Fabio Santos Duarte Lana

Future Medicine part of fsg

ARTIGO

Distribution, Recovery and concentration of Platelets and Leukocytes in L-PRP prepared by Centrifugation

- Bruna Alice Gomes de Melo
- Andréa Arruda Martins Shimojo
- Amanda Gomes Marcelino Perez
- **José Fábio Santos Duarte Lana**
- Maria Helena Andrade Santana

Publicação: 01 de Janeiro de 2018
Veículo: Colloids and Surfaces B - Biointerfaces

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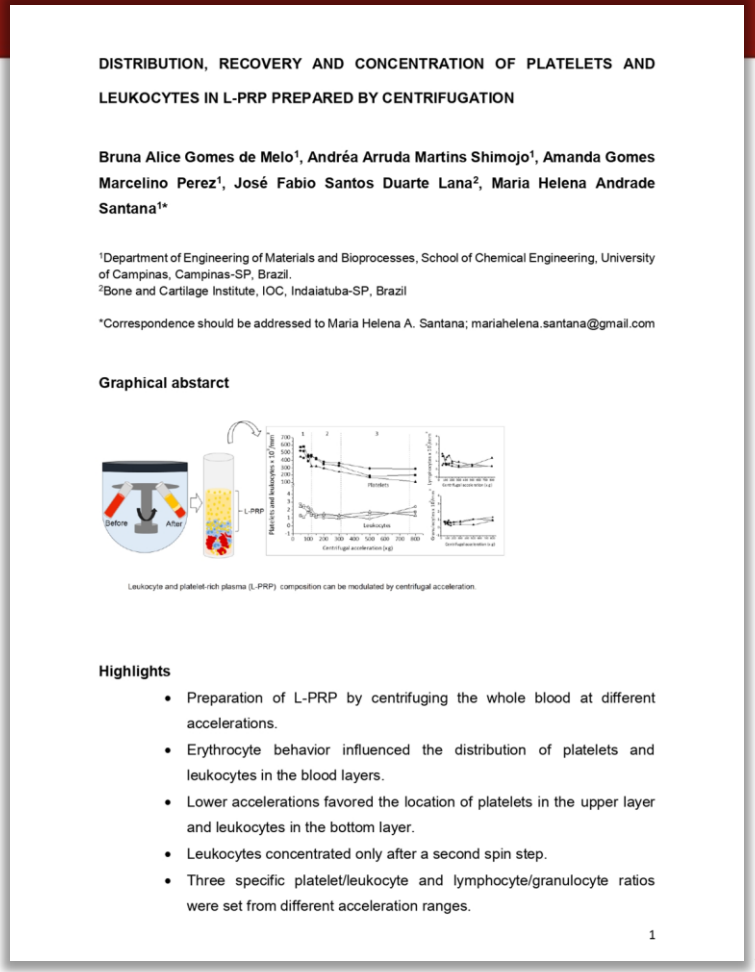

DISTRIBUTION, RECOVERY AND CONCENTRATION OF PLATELETS AND LEUKOCYTES IN L-PRP PREPARED BY CENTRIFUGATION

Bruna Alice Gomes de Melo[1], Andréa Arruda Martins Shimojo[1], Amanda Gomes Marcelino Perez[1], José Fabio Santos Duarte Lana[2], Maria Helena Andrade Santana[1]*

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Graphical abstarct

Leukocyte and platelet-rich plasma (L-PRP) composition can be modulated by centrifugal acceleration.

Highlights

- Preparation of L-PRP by centrifuging the whole blood at different accelerations.
- Erythrocyte behavior influenced the distribution of platelets and leukocytes in the blood layers.
- Lower accelerations favored the location of platelets in the upper layer and leukocytes in the bottom layer.
- Leukocytes concentrated only after a second spin step.
- Three specific platelet/leukocyte and lymphocyte/granulocyte ratios were set from different acceleration ranges.

1

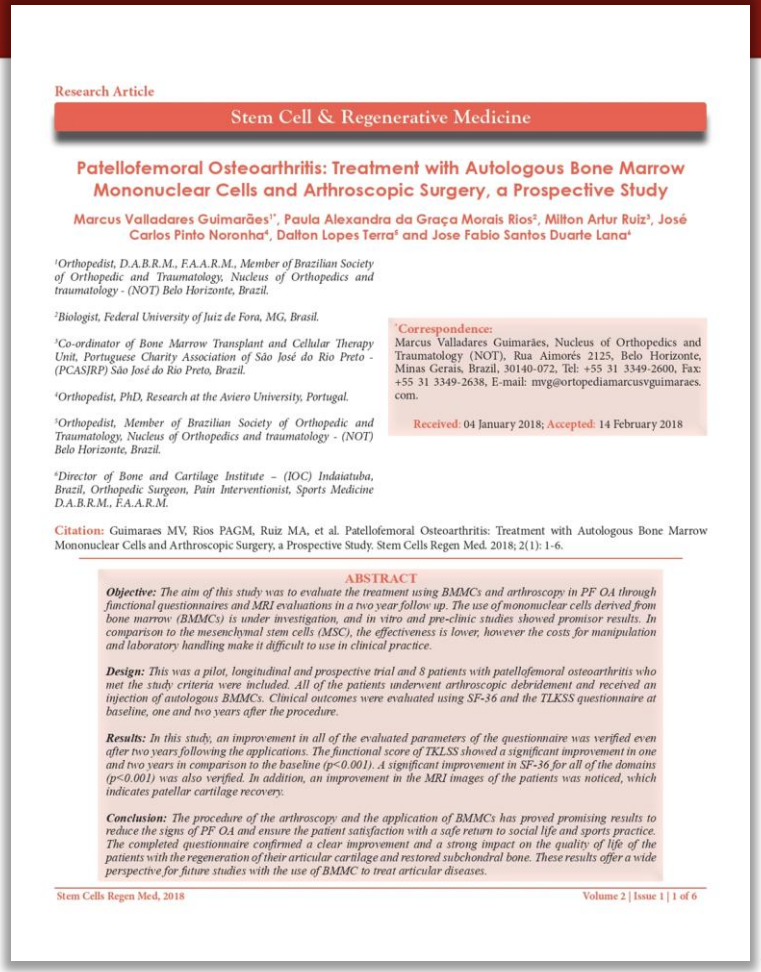
ARTIGO

Patellofemoral Osteoarthritis: Treatment with Autologous Bone Marrow Mononuclear Cells and Arthroscopic Surgery, a Prospective Study

- Marcus Valladares Guimarães
- Paula Alexandra da Graça Morais Rios
- Milton Artur Ruiz
- José Carlos Pinto Noronha
- Dalton Lopes Terra
- **José Fábio Santos Duarte Lana**

Publicação: 14 de Janeiro de 2018
Veículo: Stem Cells & Regenerative Medicine

Pesquisa completa aqui!



Research Article

Stem Cell & Regenerative Medicine

Patellofemoral Osteoarthritis: Treatment with Autologous Bone Marrow Mononuclear Cells and Arthroscopic Surgery, a Prospective Study

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ABSTRACT

Objective: *The aim of this study was to evaluate the treatment using BMMCs and arthroscopy in PF OA through functional questionnaires and MRI evaluations in a two year follow up. The use of mononuclear cells derived from bone marrow (BMMCs) is under investigation, and in vitro and pre-clinic studies showed promisor results. In comparison to the mesenchymal stem cells (MSC), the effectiveness is lower, however the costs for manipulation and laboratory handling make it difficult to use in clinical practice.*

Design: *This was a pilot, longitudinal and prospective trial and 8 patients with patellofemoral osteoarthritis who met the study criteria were included. All of the patients underwent arthroscopic debridement and received an injection of autologous BMMCs. Clinical outcomes were evaluated using SF-36 and the TLKSS questionnaire at baseline, one and two years after the procedure.*

Results: *In this study, an improvement in all of the evaluated parameters of the questionnaire was verified even after two years following the applications. The functional score of TKLSS showed a significant improvement in one and two years in comparison to the baseline ($p<0.001$). A significant improvement in SF-36 for all of the domains ($p<0.001$) was also verified. In addition, an improvement in the MRI images of the patients was noticed, which indicates patellar cartilage recovery.*

Conclusion: *The procedure of the arthroscopy and the application of BMMCs has proved promising results to reduce the signs of PF OA and ensure the patient satisfaction with a safe return to social life and sports practice. The completed questionnaire confirmed a clear improvement and a strong impact on the quality of life of the patients with the regeneration of their articular cartilage and restored subchondral bone. These results offer a wide perspective for future studies with the use of BMMC to treat articular diseases.*

ARTIGO

Correlation between Sex Hormone Deficiency and Osteoarthritis

- Macedo A
- Santos GS
- Ingrao ILG
- Vieira IFV
- Castro RB
- Huber SC
- Filho SC
- Murrell WD
- **Lana JFSD**

Publicação: 22 de Setembro de 2018
Veículo: Journal of Bone Biology and Osteoporosis

Pesquisa completa aqui!

ISSN: 2470-4539

Gratis

Review Article

Journal of Bone Biology and Osteoporosis

Correlation between Sex Hormone Deficiency and Osteoarthritis

Macedo A[1], Santos GS[1*], Ingrao ILG[1], Vieira IFV[1], Castro RB[2], Huber SC[2], Filho SC[3], Murrell WD[4] and Lana JFSD[1]

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Received date: July 18, 2018; Accepted date: September 17, 2018; Published date: September22, 2018

Abstract

This literature review explores recent and past investigations carried out by researchers in various settings pertaining to the orthopaedic field of medicine, in attempts to show a possible connection between the deficit in sex hormone levels and the potential consequences it brings about on orthopaedic health, namely, osteoarthritis. There is some evidence in the literature suggesting that suboptimal concentrations of steroid hormones can negatively impact bone health, making it more susceptible to physical injury, especially when the hormone in question is estrogen. Several studies have shown that this biomolecule is quite essential to human health due to its effects on not only sexual development and function but also on bone metabolism, in both men and women. Investigations revolving around estrogenic compounds reveal their significance in physical capacitation of adult individuals, since it has already been found that estrogens play a pivotal role on bone maintenance by directly interacting with osteocytes, osteoblasts, osteoclasts and even T-cells, to name a few examples. Large scale studies also bring up plausible evidence by evaluating the links between measured sex steroid concentrations and incidence of osteoarthritic joint replacement in adults. Taking that into consideration, there is sufficient motivation to look into hormonal fluctuation in adult individuals, calling for suitable medical intervention in order to keep a patient's health under control, avoiding and even treating the detrimental effects caused by the deficiency of certain steroid hormones.

Keywords: Osteoarthritis, Estrogen, Testosterone, Bone metabolism, Menopause

Introduction

Osteoarthritis (OA) is a major degenerative joint disease which can affect more than one quarter of the global population in individuals over the age of 18. This disease is typically defined by the following observations: progressive loss of articular cartilage, thickening of the subchondral bone, and formation of osteophyte, significant inflammation of the synovial as well as degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule. Risk factors for OA encompass joint injury, obesity, aging and even genetic predisposition [1-3]. The pathological changes involved in the progression of OA are caused by biomechanical forces as well as multiple autocrine, paracrine and endocrine cellular events which all contribute to perturbations of tissue homeostasis within the affected joint [4],[5]. Gonadal steroid hormones, such as Estrogen (E) and Testosterone (T), for example, are molecules that are biosynthesized in the body and play a key role in sexual development and reproduction, which

ARTIGO

Treatment of male pattern alopecia with platelet-rich plasma: A double-blind controlled study with analysis of platelet number and growth factor levels

- Bruno L. Rodrigues
- Silmara A. L. Montalvão
- Rebeca B. B. Cancela
- Francesca A. R. Silva
- Aline Urban Stephany C. Huber
- José Luiz R. C. Junior
- **José Fábio S. D. Lana**
- Joyce M. Annichinno-Bizzacchi

Publicação: 02 de Outubro de 2018
Veículo: Elsevier - Journal of the American Academy of Dermatology

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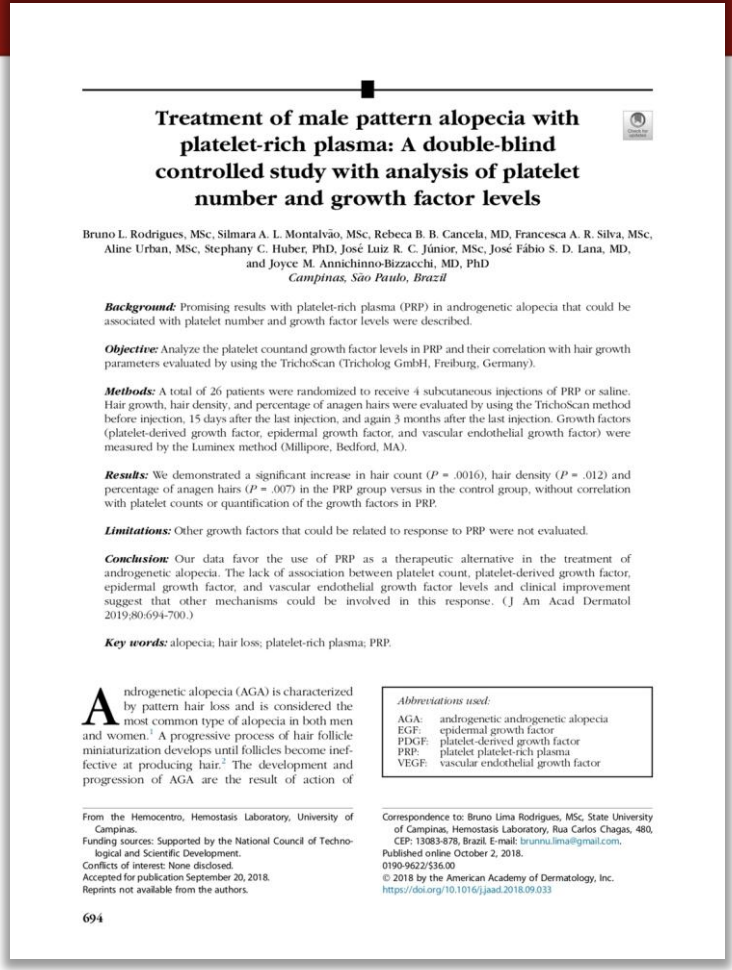

Treatment of male pattern alopecia with platelet-rich plasma: A double-blind controlled study with analysis of platelet number and growth factor levels

Bruno L. Rodrigues, MSc, Silmara A. L. Montalvão, MSc, Rebeca B. B. Cancela, MD, Francesca A. R. Silva, MSc, Aline Urban, MSc, Stephany C. Huber, PhD, José Luiz R. C. Júnior, MSc, José Fábio S. D. Lana, MD, and Joyce M. Annichinno-Bizzacchi, MD, PhD
Campinas, São Paulo, Brazil

Background: Promising results with platelet-rich plasma (PRP) in androgenetic alopecia that could be associated with platelet number and growth factor levels were described.

Objective: Analyze the platelet countand growth factor levels in PRP and their correlation with hair growth parameters evaluated by using the TrichoScan (Tricholog GmbH, Freiburg, Germany).

Methods: A total of 26 patients were randomized to receive 4 subcutaneous injections of PRP or saline. Hair growth, hair density, and percentage of anagen hairs were evaluated by using the TrichoScan method before injection, 15 days after the last injection, and again 3 months after the last injection. Growth factors (platelet-derived growth factor, epidermal growth factor, and vascular endothelial growth factor) were measured by the Luminex method (Millipore, Bedford, MA).

Results: We demonstrated a significant increase in hair count ($P = .0016$), hair density ($P = .012$) and percentage of anagen hairs ($P = .007$) in the PRP group versus in the control group, without correlation with platelet counts or quantification of the growth factors in PRP.

Limitations: Other growth factors that could be related to response to PRP were not evaluated.

Conclusion: Our data favor the use of PRP as a therapeutic alternative in the treatment of androgenetic alopecia. The lack of association between platelet count, platelet-derived growth factor, epidermal growth factor, and vascular endothelial growth factor levels and clinical improvement suggest that other mechanisms could be involved in this response. (J Am Acad Dermatol 2019;80:694-700.)

Key words: alopecia; hair loss; platelet-rich plasma; PRP.

Androgenetic alopecia (AGA) is characterized by pattern hair loss and is considered the most common type of alopecia in both men and women.[1] A progressive process of hair follicle miniaturization develops until follicles become ineffective at producing hair.[2] The development and progression of AGA are the result of action of

Abbreviations used:

AGA:	androgenetic androgenetic alopecia
EGF:	epidermal growth factor
PDGF:	platelet-derived growth factor
PRP:	platelet platelet-rich plasma
VEGF:	vascular endothelial growth factor

From the Hemocentro, Hemostasis Laboratory, University of Campinas.
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ARTIGO

Nutritional, metabolic and genetic considerations to optimise regenerative medicine outcome for knee osteoarthritis

- Kholoud Hafsi
- Janine McKay
- Jinjie Li
- **José Fábio Lana**
- Alex Macedo
- Gabriel Silva Santos
- William D. Murrell

Publicação: 15 de Outubro de 2018
Veículo: Elsevier - Journal of Clinical Orthopaedics and Trauma

Pesquisa completa aqui!

Journal of Clinical Orthopaedics and Trauma 10 (2019) 2–8

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Nutritional, metabolic and genetic considerations to optimise regenerative medicine outcome for knee osteoarthritis

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ARTICLE INFO

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ABSTRACT

Knee osteoarthritis (KOA) is a multifactorial degenerative disorder of joints, affecting the world's population over the age of 65 and with a higher prevalence in females. KOA is responsible for many age associated joint problems such as stiffness and pain. Conventional methods for managing KOA such as nonsteroidal anti-inflammatory drugs (NSAID) may not improve pain or alter the disease progression and may have adverse side effects. Non-pharmacological management of OA is fundamental to management of functional limitations and provides effective symptom relief but has not shown that disease progression can be altered. Regenerative medicine is a relatively new approach which aims to induce cellular regeneration and promote self-healing through minimally invasive methods. The use of regenerative medicine slowed the progression of KOA and revealed significant improvements, yet further investigations are required to optimize the outcomes. Nutritional and metabolic aspects such as supplementations, vitamins and minerals were proven to have an impact on the progression of KOA. Genetic variations are rapidly inspected to identify any potential influence of these variations in the predisposition and diagnosis of KOA. Further supporting evidence suggests the potential influence of metabolic, nutritional and genetic aspects in optimizing the outcomes of regenerative medicine in the management of KOA.

1. Introduction

Osteoarthritis (OA) is the most common chronic joint disorder and the main cause of joint pain, loss of function and disability in adults. As reported in research OA is prevalent in individuals above the age of 65 years old.[1] 80% of the population over the age of 75 years suffers from Knee osteoarthritis (KOA).[1,2] KOA is a degenerative inflammatory disease disturbing various components of the knee and hypertrophy of the joint capsule such as the articular cartilage, synovial joint lining, periarticular bone and adjacent supporting fibrocartilaginous and musculature structures.[1,3] Augmented concentrations of activated proteins and cytokines is reported with the progressive loss in the articular cartilage, subchondral bone and chondrocytes.[1,4] The diagnosis of KOA utilise a combination of anatomic analysis and imaging to identify KOA-induced structural damage and classify the patient's condition to mild, moderate or severe KOA accordingly.[5]

KOA is a multifactorial disease. Intrinsic and extrinsic factors interact and contribute at various levels to the evolution of this multifactorial disease (Fig. 1). The pathogenesis of KOA is influenced by several genetic factors as well as environmental factors related to molecular pathways that contribute to articular injury.[5] While the knowledge of the main cause of KOA is insufficient, age, sex and injury's link to KOA has been established among ethnicities.[2]

Chronic disease such as KOA, is progressive and is preceded by a period of declining function in one or more of the biological systems. Restoring health requires improving specific dysfunctions that have contributed to the disease state. Conventional treatments have only showed limited clinical benefits. Current pharmacological treatments such as nonsteroidal anti-inflammatory drugs

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ARTIGO

The Role of Thyroid Hormones on Management of Cartilaginous Joint Disorders

- Gabriel Ohana Marques Azzini
- Silvia Beatriz Coutinho Visoni
- Gabriel Silva Santos
- Stephany Cares Huber
- Alex Macedo
- Icaro Lanzoni Gallo Ingrao
- **José Fábio Santos Duarte Lana**

Publicação: 14 de Novembro 2018
Veículo: JP - Novel Techniques in Arthritis & Bone Research

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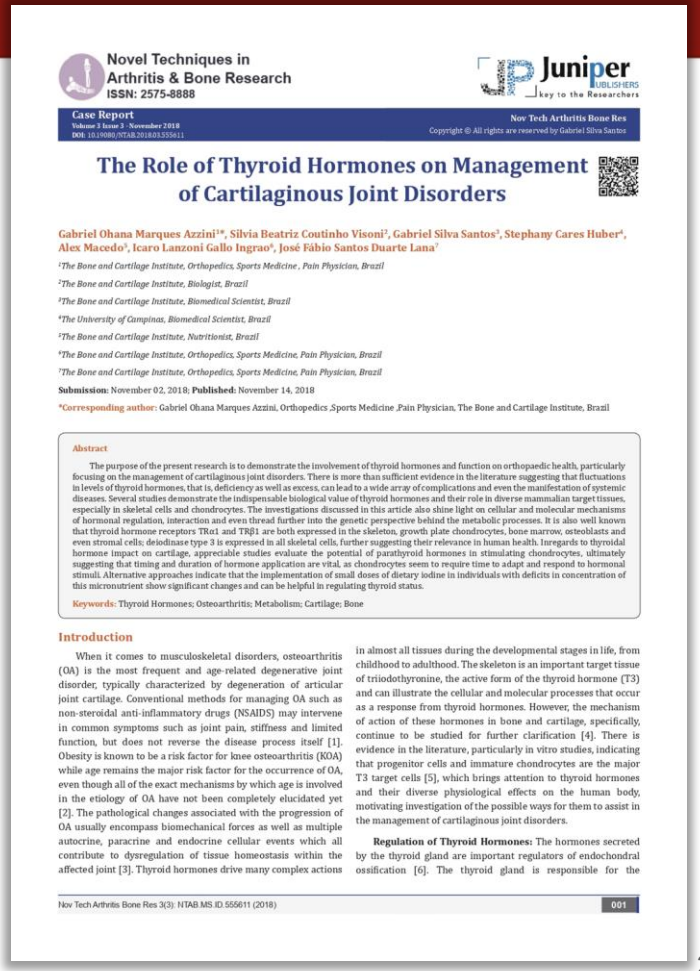

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Case Report
Volume 3 Issue 3 - November 2018
DOI: 10.19080/NTAB.2018.03.555611

Nov Tech Arthritis Bone Res

The Role of Thyroid Hormones on Management of Cartilaginous Joint Disorders

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Abstract

The purpose of the present research is to demonstrate the involvement of thyroid hormones and function on orthopaedic health, particularly focusing on the management of cartilaginous joint disorders. There is more than sufficient evidence in the literature suggesting that fluctuations in levels of thyroid hormones, that is, deficiency as well as excess, can lead to a wide array of complications and even the manifestation of systemic diseases. Several studies demonstrate the indispensable biological value of thyroid hormones and their role in diverse mammalian target tissues, especially in skeletal cells and chondrocytes. The investigations discussed in this article also shine light on cellular and molecular mechanisms of hormonal regulation, interaction and even thread further into the genetic perspective behind the metabolic processes. It is also well known that thyroid hormone receptors TRα1 and TRβ1 are both expressed in the skeleton, growth plate chondrocytes, bone marrow, osteoblasts and even stromal cells; deiodinase type 3 is expressed in all skeletal cells, further suggesting their relevance in human health. Inregards to thyroidal hormone impact on cartilage, appreciable studies evaluate the potential of parathyroid hormones in stimulating chondrocytes, ultimately suggesting that timing and duration of hormone application are vital, as chondrocytes seem to require time to adapt and respond to hormonal stimuli. Alternative approaches indicate that the implementation of small doses of dietary iodine in individuals with deficits in concentration of this micronutrient show significant changes and can be helpful in regulating thyroid status.

Keywords: Thyroid Hormones; Osteoarthritis; Metabolism; Cartilage; Bone

Introduction

When it comes to musculoskeletal disorders, osteoarthritis (OA) is the most frequent and age-related degenerative joint disorder, typically characterized by degeneration of articular joint cartilage. Conventional methods for managing OA such as non-steroidal anti-inflammatory drugs (NSAIDS) may intervene in common symptoms such as joint pain, stiffness and limited function, but does not reverse the disease process itself [1]. Obesity is known to be a risk factor for knee osteoarthritis (KOA) while age remains the major risk factor for the occurrence of OA, even though all of the exact mechanisms by which age is involved in the etiology of OA have not been completely elucidated yet [2]. The pathological changes associated with the progression of OA usually encompass biomechanical forces as well as multiple autocrine, paracrine and endocrine cellular events which all contribute to dysregulation of tissue homeostasis within the affected joint [3]. Thyroid hormones drive many complex actions in almost all tissues during the developmental stages in life, from childhood to adulthood. The skeleton is an important target tissue of triiodothyronine, the active form of the thyroid hormone (T3) and can illustrate the cellular and molecular processes that occur as a response from thyroid hormones. However, the mechanism of action of these hormones in bone and cartilage, specifically, continue to be studied for further clarification [4]. There is evidence in the literature, particularly in vitro studies, indicating that progenitor cells and immature chondrocytes are the major T3 target cells [5], which brings attention to thyroid hormones and their diverse physiological effects on the human body, motivating investigation of the possible ways for them to assist in the management of cartilaginous joint disorders.

Regulation of Thyroid Hormones: The hormones secreted by the thyroid gland are important regulators of endochondral ossification [6]. The thyroid gland is responsible for the

ARTIGO

Orthobiologic Treatment for Knee Osteoarthritis: A Cost Effectiveness Choice

- **José Fábio Santos Duarte Lana**
- Renato Bevilacqua de Castro
- Bruno Lima Rodrigues
- Carolina Caliari Oliveira
- Stephany Cares Huber
- Nelson Foresto Lizier
- William D Murrel
- Mathew Nicholls

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Veículo: BioMedical - Journal of Scientific & Technical Research

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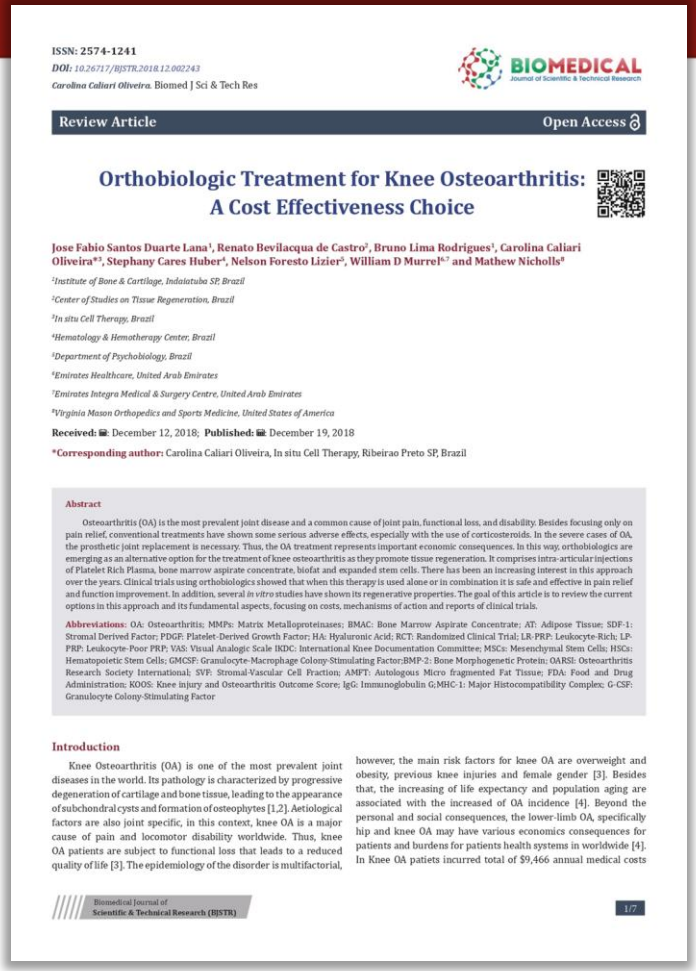

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Carolina Caliari Oliveira. Biomed J Sci & Tech Res

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Review Article Open Access

Orthobiologic Treatment for Knee Osteoarthritis: A Cost Effectiveness Choice

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Abstract

Osteoarthritis (OA) is the most prevalent joint disease and a common cause of joint pain, functional loss, and disability. Besides focusing only on pain relief, conventional treatments have shown some serious adverse effects, especially with the use of corticosteroids. In the severe cases of OA, the prosthetic joint replacement is necessary. Thus, the OA treatment represents important economic consequences. In this way, orthobiologics are emerging as an alternative option for the treatment of knee osteoarthritis as they promote tissue regeneration. It comprises intra-articular injections of Platelet Rich Plasma, bone marrow aspirate concentrate, biofat and expanded stem cells. There has been an increasing interest in this approach over the years. Clinical trials using orthobiologics showed that when this therapy is used alone or in combination it is safe and effective in pain relief and function improvement. In addition, several *in vitro* studies have shown its regenerative properties. The goal of this article is to review the current options in this approach and its fundamental aspects, focusing on costs, mechanisms of action and reports of clinical trials.

Abbreviations: OA: Osteoarthritis; MMPs: Matrix Metalloproteinases; BMAC: Bone Marrow Aspirate Concentrate; AT: Adipose Tissue; SDF-1: Stromal Derived Factor; PDGF: Platelet-Derived Growth Factor; HA: Hyaluronic Acid; RCT: Randomized Clinical Trial; LR-PRP: Leukocyte-Rich; LP-PRP: Leukocyte-Poor PRP; VAS: Visual Analogic Scale IKDC: International Knee Documentation Committee; MSCs: Mesenchymal Stem Cells; HSCs: Hematopoietic Stem Cells; GMCSF: Granulocyte-Macrophage Colony-Stimulating Factor;BMP-2: Bone Morphogenetic Protein; OARSI: Osteoarthritis Research Society International; SVF: Stromal-Vascular Cell Fraction; AMFT: Autologous Micro fragmented Fat Tissue; FDA: Food and Drug Administration; KOOS: Knee injury and Osteoarthritis Outcome Score; IgG: Immunoglobulin G;MHC-1: Major Histocompatibility Complex; G-CSF: Granulocyte Colony-Stimulating Factor

Introduction

Knee Osteoarthritis (OA) is one of the most prevalent joint diseases in the world. Its pathology is characterized by progressive degeneration of cartilage and bone tissue, leading to the appearance of subchondral cysts and formation of osteophytes [1,2]. Aetiological factors are also joint specific, in this context, knee OA is a major cause of pain and locomotor disability worldwide. Thus, knee OA patients are subject to functional loss that leads to a reduced quality of life [3]. The epidemiology of the disorder is multifactorial, however, the main risk factors for knee OA are overweight and obesity, previous knee injuries and female gender [3]. Besides that, the increasing of life expectancy and population aging are associated with the increased of OA incidence [4]. Beyond the personal and social consequences, the lower-limb OA, specifically hip and knee OA may have various economics consequences for patients and burdens for patients health systems in worldwide [4]. In Knee OA patiets incurred total of $9,466 annual medical costs

ARTIGO

Leukocyte-rich PRP for knee osteoarthritis: Current concepts

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- Icaro Lanzoni Gallo Ingrao
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Leukocyte-rich PRP for knee osteoarthritis: Current concepts

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ABSTRACT

Knee osteoarthritis is a major painful and debilitating orthopaedic disease affecting a large number of adult individuals on a global scale. Over the years, this severe condition has been widely studied and while many alternatives have been utilized, platelet-rich plasma (PRP) remains one of the most popular solutions among researchers and clinicians alike. While there are different formulations and techniques involved in the preparation of PRP, produced either manually or via the use of commercial kits, the presence of leukocytes in a PRP mixture is a factor that raises concern due to their well-known pro-inflammatory activity. Although it is reasonable to worry about this, it should be taken into consideration that in order for the healing process to occur, the inflammatory phase is necessary. Leukocytes present in the inflammatory phase release both pro and anti-inflammatory molecules and, when combined with activated platelets, their potential increases. Additionally, due to the macrophage's plasticity to switch from the subtype 1 to subtype 2, it is suggested that the inclusion of the components from the buffy coat layer in a PRP mixture, classifying it as leukocyte-rich platelet-rich plasma or L-PRP, may provide benefits instead of detriments, from a standpoint of the regenerative potential of PRP.

1. Introduction

Osteoarthritis (OA), the most common progressive joint disease involving cartilage and surrounding tissues[1] is generally characterized by joint inflammation and a reparative bone response. It is one of the top five most disabling conditions, affecting more than one-third of the elderly population above 65 years of age, with global estimates reaching a number greater than 100 million individuals affected by this disease.[2] Knee osteoarthritis (KOA), in particular, is commonly attributed to aging and obesity and has doubled in prevalence since the mid-20th century.[3] This disease is typically defined by progressive loss of articular cartilage, thickening of the subchondral bone, formation of osteophytes, significant inflammation of the synovium as well as degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule.[4] Risk factors for OA encompass joint injury, obesity, aging and even genetic predisposition. Since the OA microenvironment becomes increasingly catabolic and destructive, continuous research with the rising popularity of platelet-rich plasma (PRP) therapy revealed that platelet alpha-granules which contain and release numerous growth factors such as hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor-b (TGF-β), as examples, can be beneficial in modulating the status of the disease.[5] On top of that, investigations regarding leukocyte content in PRP formulations and the potential effects on osteoarthritis treatment have caused some controversy in the literature due to the fact the these cells, especially neutrophils, are known to cause inflammation by driving the inflammatory phase of wound healing. Although preoccupation still exists regarding the applications of leukocyte-rich platelet-rich plasma (L-PRP), some studies point out that apart from an anti-infectious property, leukocytes produce large amounts of VEGF, to illustrate a few of the multiple benefits attributed to this cell type.[6] This review provides some insights on the possible cellular mechanisms whereby L-PRP may act to manage the deteriorated microenvironment generated by osteoarthritis, particularly knee osteoarthritis (KOA), and the potential benefits of their involvement.

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ARTIGO

Impact on the quality of life of patients suffering from osteoarthritis of the knee after intra-articular administration of bone marrow mononuclear cells

- Marcus Valadares Guimarães
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- Paula Alexandra da Graça Morais

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Clinical and Medical Investigations

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Research Article ISSN: 2398-5763

Impact on the quality of life of patients suffering from osteoarthritis of the knee after intra-articular administration of bone marrow mononuclear cells

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Abstract

Objective: The aim of this study was to evaluate the combined treatment of BMMCs alone or in combination of arthroscopic debridement and lavage in treatment of knee OA through resonance image and quality of life questionnaire. In comparison to the mesenchymal stem cells (MSC), the effectiveness is lower, however the costs for manipulation and laboratory handling make it difficult to use in clinical practice.

Design: This was a pilot, longitudinal and prospective trial with two years of follow-up. Twenty-one patients with patellofemoral osteoarthritis who met the study criteria were included. The patients were divided into three groups: BMMCs+Arthroscopy; BMMCs+lavage; BMMC. Clinical outcomes were evaluated using SF-36 questionnaire at baseline and two years after the procedure.

Results: In this study, it was verified a high recovery of BMMCs and platelets, especially with manual separation. It was not observed differences in SF-36 when comparing the three groups, however the evaluation of SF-36 baseline and two years of follow-up in each one of the three groups, it was showed an improvement in 3-4 parameters. The MRI showed an improvement in the stroke, subchondral bone and cartilage size in the patella and femur.

Conclusion: This study demonstrated that OA showed a significant improvement, measured by quality life questionnaire, only with the use of BMMCs, showing no improvement with the combination of arthroscopy or joint lavage. In this way, the use of BMMC's is well accepted, a presented impact on parameters of SF-36. None of the patients underwent total knee arthroplasty. A study with a higher number of patients is of great value to assess the safety and efficacy of BMMC's application.

Introduction

Articular cartilage has a limited intrinsic capacity to regenerate spontaneously after injury, often leading to pain and disability. It is generally believed that cartilage lesions progress to osteoarthritis (OA). OA of the knee is one of the most chronic degenerative joints diseases, affecting the quality of life of patient. Prompt intervention for symptomatic lesions make possible prevention of evolution to OA as well as to provide symptom relief. Conventional treatment modalities may be useful for relief of symptoms in the short term; however, they do not restore the natural articular cartilage integrity or prevent the deterioration [1]. In addition, the surgery for knee replacement provides a solution for severe OA [2]. The conservative nonsurgical treatments include analgesics, nonsteroid and steroid anti-inflammatory drugs and corticosteroids [3,4]. When the conservative treatment fails to control the symptoms and functional limitations occur, surgery should be considered to treat the cartilage lesion and the anatomical abnormalities. Conventional methods used to regenerate anormalies of the articular cartilage include microfractures, multiple perforation, abrasion and mosaicoplasty, with limited results [5].

Orthobiologics is a thriving area of research and development, aimed specifically at preventing further degeneration and disease by restoring native biology, structure, and function. Cell-based therapy is a form of regenerative medicine that introduces new cells to repair damaged tissue [1]. Nowadays, there are a variety of orthobiologics such as: whole blood therapy, traditional prolotherapy, platelet rich plasma (PRP), autologous conditioned plasma (ACP) or autologous conditioned serum, bone marrow aspirate, adipose biocellular autografts, allograft of mesenchymal stem cells are the most well-studied and prevalent grafts of current use [6]. In this study we focus on autologous mononuclear cells obtained from bone marrow (BMMC). In cell therapy, the majority of studies have used mesenchymal stem cells derived from bone marrow (BMSC). It's important to note that, the BMMCs, enriched with BMSCs have shown to be beneficial [7]. Previous clinical trials have demonstrated beneficial effects in osteonecrosis of femoral head, relieving pain and prevents the progression of osteonecrosis. The number of cells used increased 3 folds basal number, reaching 35.2 x 10^6 cells /mL [8]. We published a study evaluating the use of BMMCs and arthroscopy to treat patellofemoral osteoarthritis and verified promising results, reducing signs of patellofemoral AO and ensure the patient satisfaction with a safe return to social life and sports and improvement in functional scores, restoring the articular cartilage of subchondral bone [9]. However, the use of BMMCs for OA is not

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ARTIGO

Leukocyte-rich PRP versus leukocyte-poor PRP - The role of monocyte/macrophage function in the healing cascade

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- Claudia H. Tambeli
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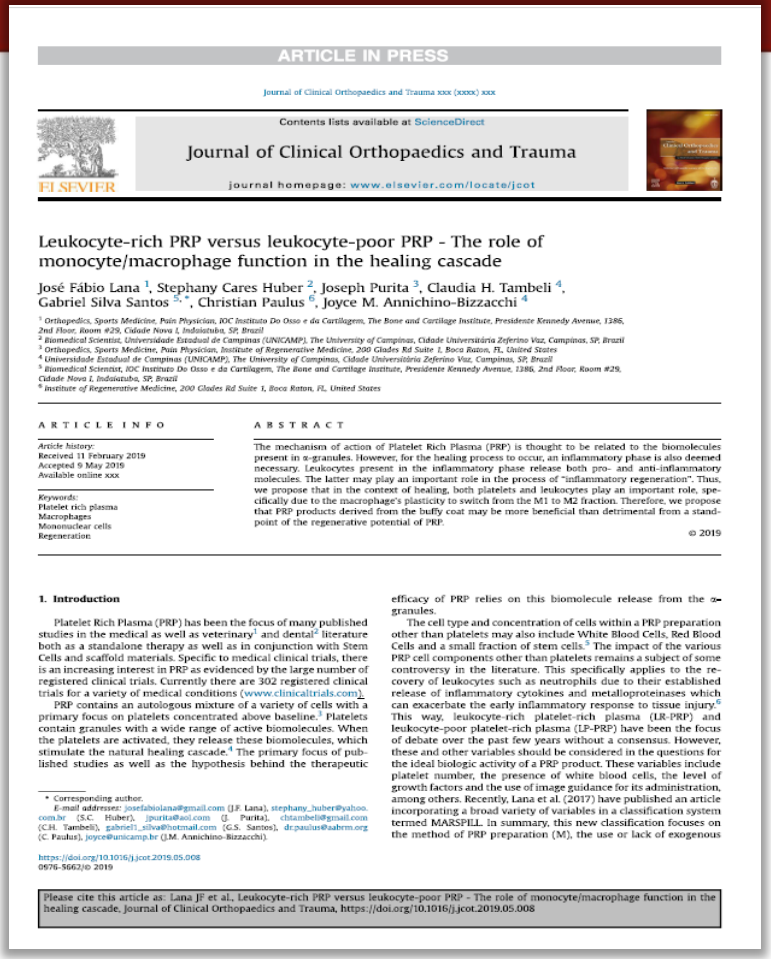

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Leukocyte-rich PRP versus leukocyte-poor PRP - The role of monocyte/macrophage function in the healing cascade

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ABSTRACT

The mechanism of action of Platelet Rich Plasma (PRP) is thought to be related to the biomolecules present in α-granules. However, for the healing process to occur, an inflammatory phase is also deemed necessary. Leukocytes present in the inflammatory phase release both pro- and anti-inflammatory molecules. The latter may play an important role in the process of "inflammatory regeneration". Thus, we propose that in the context of healing, both platelets and leukocytes play an important role, specifically due to the macrophage's plasticity to switch from the M1 to M2 fraction. Therefore, we propose that PRP products derived from the buffy coat may be more beneficial than detrimental from a standpoint of the regenerative potential of PRP.

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1. Introduction

Platelet Rich Plasma (PRP) has been the focus of many published studies in the medical as well as veterinary[1] and dental[2] literature both as a standalone therapy as well as in conjunction with Stem Cells and scaffold materials. Specific to medical clinical trials, there is an increasing interest in PRP as evidenced by the large number of registered clinical trials. Currently there are 302 registered clinical trials for a variety of medical conditions (www.clinicaltrials.com).

PRP contains an autologous mixture of a variety of cells with a primary focus on platelets concentrated above baseline.[3] Platelets contain granules with a wide range of active biomolecules. When the platelets are activated, they release these biomolecules, which stimulate the natural healing cascade.[4] The primary focus of published studies as well as the hypothesis behind the therapeutic efficacy of PRP relies on this biomolecule release from the α-granules.

The cell type and concentration of cells within a PRP preparation other than platelets may also include White Blood Cells, Red Blood Cells and a small fraction of stem cells.[5] The impact of the various PRP cell components other than platelets remains a subject of some controversy in the literature. This specifically applies to the recovery of leukocytes such as neutrophils due to their established release of inflammatory cytokines and metalloproteinases which can exacerbate the early inflammatory response to tissue injury.[6] This way, leukocyte-rich platelet-rich plasma (LR-PRP) and leukocyte-poor platelet-rich plasma (LP-PRP) have been the focus of debate over the past few years without a consensus. However, these and other variables should be considered in the questions for the ideal biologic activity of a PRP product. These variables include platelet number, the presence of white blood cells, the level of growth factors and the use of image guidance for its administration, among others. Recently, Lana et al. (2017) have published an article incorporating a broad variety of variables in a classification system termed MARSPILL. In summary, this new classification focuses on the method of PRP preparation (M), the use or lack of exogenous

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ARTIGO

Procedures Guided by Ultrasonography in Injectable Treatments in Knee, Hip and Shoulder Pathologies

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- Sergio Ricardo Neto Breno Pazinatto Antoni
- **José Fábio Lana**
- Fernanda Santiago Bassora

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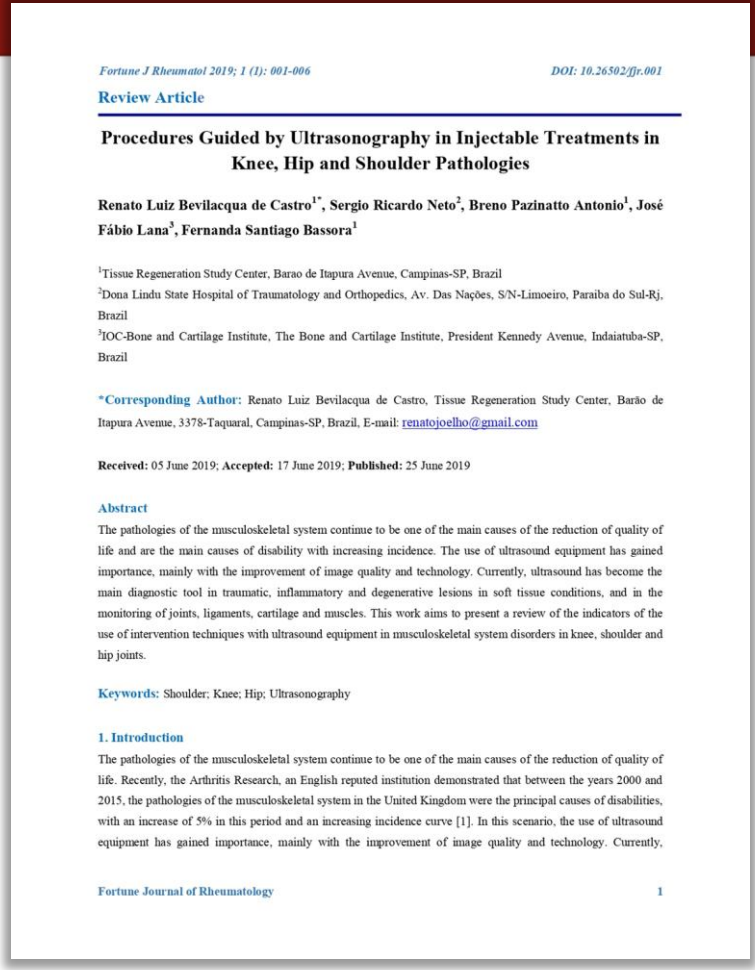

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Review Article

Procedures Guided by Ultrasonography in Injectable Treatments in Knee, Hip and Shoulder Pathologies

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Abstract

The pathologies of the musculoskeletal system continue to be one of the main causes of the reduction of quality of life and are the main causes of disability with increasing incidence. The use of ultrasound equipment has gained importance, mainly with the improvement of image quality and technology. Currently, ultrasound has become the main diagnostic tool in traumatic, inflammatory and degenerative lesions in soft tissue conditions, and in the monitoring of joints, ligaments, cartilage and muscles. This work aims to present a review of the indicators of the use of intervention techniques with ultrasound equipment in musculoskeletal system disorders in knee, shoulder and hip joints.

Keywords: Shoulder; Knee; Hip; Ultrasonography

1. Introduction

The pathologies of the musculoskeletal system continue to be one of the main causes of the reduction of quality of life. Recently, the Arthritis Research, an English reputed institution demonstrated that between the years 2000 and 2015, the pathologies of the musculoskeletal system in the United Kingdom were the principal causes of disabilities, with an increase of 5% in this period and an increasing incidence curve [1]. In this scenario, the use of ultrasound equipment has gained importance, mainly with the improvement of image quality and technology. Currently,

ARTIGO

Centrifugation Conditions in the L-PRP Preparation Affect Soluble Factors Release and Mesenchymal Stem Cell Proliferation in Fibrin Nanofibers

- Bruna Alice Gomes de Melo
- Ângela Cristina Malheiros Luzo
- **José Fábio Santos Duarte Lana**
- Maria Helena Andrade Santana

Publicação: 27 de Julho de 2019
Veículo: MDPI - Molecules

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molecules

MDPI

Article

Centrifugation Conditions in the L-PRP Preparation Affect Soluble Factors Release and Mesenchymal Stem Cell Proliferation in Fibrin Nanofibers

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Abstract: Leukocyte and platelet-rich plasma (L-PRP) is an autologous product that when activated forms fibrin nanofibers, which are useful in regenerative medicine. As an important part of the preparation of L-PRP, the centrifugation parameters may affect the release of soluble factors that modulate the behavior of the cells in the nanofibers. In this study, we evaluated the influences of four different centrifugation conditions on the concentration of platelets and leukocytes in L-PRP and on the anabolic/catabolic balance of the nanofiber microenvironment. Human adipose-derived mesenchymal stem cells (h-AdMSCs) were seeded in the nanofibers, and their viability and growth were evaluated. L-PRPs prepared at 100× *g* and 100 + 400× *g* released higher levels of transforming growth factor (TGF)-β1 and platelet-derived growth factor (PDGF)-BB due to the increased platelet concentration, while inflammatory cytokines interleukin (IL)-8 and tumor necrosis factor (TNF)-α were more significantly released from L-PRPs prepared via two centrifugation steps (100 + 400× *g* and 800 + 400× *g*) due to the increased concentration of leukocytes. Our results showed that with the exception of nanofibers formed from L-PRP prepared at 800 + 400× *g*, all other microenvironments were favorable for h-AdMSC proliferation. Here, we present a reproducible protocol for the standardization of L-PRP and fibrin nanofibers useful in clinical practices with known platelet/leukocyte ratios and in vitro evaluations that may predict in vivo results.

Keywords: platelet; leukocyte; L-PRP; centrifugation; fibrin; nanofiber; growth factor; cytokine; mesenchymal stem cells

1. Introduction

In the past few years, the benefits of autologous leukocyte- and platelet-rich plasma (L-PRP) have been evidenced in the treatment of many types of diseases [1–6]. Aside from growth factors (GFs) released from the platelets' alpha granules, L-PRP contains inflammatory cytokines secreted from leukocytes that act in synergy to modulate the migration, proliferation, and differentiation of autologous cells through different pathways that lead to tissue regeneration [7–11]. Depending on the site, the degree of the injury (acute or chronic), and treatment phase (early or late stage of healing), the leukocyte fraction must be adjusted from poor-leukocyte PRP (P-PRP) to L-PRP [12–14]. Modern classifications systems consider the platelet and leukocyte levels, aside from other conditions, such as the number of centrifugation spins, activation, the presence of erythrocytes, and guided applications [15–18].

ARTIGO

Association of Platelet-Rich Plasma and Auto-Crosslinked Hyaluronic Acid Microparticles: Approach for Orthopedic Application

- Andréa Arruda Martins Shimojo
- Adriana da Silva Santos Duarte
- **José Fábio Santos Duarte Lana**
- Ângela Cristina Malheiros Luzo
- Ana Rita Fernandes
- Elena Sanchez-Lopez
- Eliana Barbosa Souto
- Maria Helena Andrade Santana

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Veículo: MDPI - Polymers

Pesquisa completa aqui!

polymers

MDPI

Article

Association of Platelet-Rich Plasma and Auto-Crosslinked Hyaluronic Acid Microparticles: Approach for Orthopedic Application

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Abstract: Platelet-rich plasma (PRP) associated with high molecular weight hyaluronic acid (HA) has been clinically used for tissue regeneration in orthopedics. Despite the recognized beneficial clinical outcomes (e.g., early pain control, improvement of patients' functional limitation and longer-term effectiveness compared to PRP and HA alone in mild and moderate osteoarthritis treatments), its use is still challenging and controversial due to lack of standardization of association practical protocols. Moreover, most studies neglect the matrix structure, that generates the ultimate properties of the association among platelets, fibrin network and the microparticles. In the present work, we aimed to analyze the influence of the PRP/HA association with a controlled matrix structure on the stability, rheological behavior, release of growth factors and in vitro proliferation of human adipose-derived mesenchymal cells (h-AdMSCs). The attenuation of the negative charge of HA was also evaluated. Pure PRP (P-PRP) (i.e., plasma enriched with platelets and poor in leukocytes) was prepared by centrifugation and activated with serum and calcium chloride (AP-PRP). Autocrosslinked hyaluronic acid (AHA) was prepared by organocatalyzed auto-esterification and structured in microparticles (MPAHA) by shearing. The attenuation of the negative charge of MPAHA was performed with chitosan (CHT) by polyelectrolyte complexation yielding MPAHA-CHT. The results showed that microparticles (MPs) have viscoelastic properties, extrusion force and swelling ratio appropriate for injectable applications. The association of AP-PRP with the controlled structure of MPAHA and MPAHA-CHT formed a matrix composed of platelets and of a fibrin network with fibers around 160 nm located preferably on the surface of the MPs with an average diameter of 250 µm. Moreover, AP-PRP/MPAHA and AP-PRP/MPAHA-CHT associations were non-toxic and supported controlled growth factor (PDGF-AB and TGF-β1) release and in vitro proliferation of h-AdMSC with a similar pattern to that of AP-PRP alone. The best h-AdMSC proliferation was obtained with the AP-PRP/MPAHA-CHT75:25 indicating that the charge attenuation improved the cell

ARTIGO

Hyaluronic acid and fibrin from L-PRP form semi-IPNs with tunable properties suitable for use in regenerative medicine

- Bruna Alice Gomes de Melo
- Carla Giometti França
- José Luis Dávila
- NilzaAlzira Batista
- Carolina Caliari-Oliveira
- Marcos Akira d'Ávila
- Ângela Cristina Malheiros Luzo
- **José Fábio Santos Duarte Lana**
- Maria Helena Andrade Santana

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Hyaluronic acid and fibrin from L-PRP form semi-IPNs with tunable properties suitable for use in regenerative medicine

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ABSTRACT

Autologous leukocyte- and platelet-rich plasma (L-PRP) combined with hyaluronic acid (HA) has been widely used in local applications for cartilage and bone regeneration. The association between L-PRP and HA confers structural and rheological changes that differ among individual biomaterials but has not been investigated. Therefore, the standardization and characterization of L-PRP-HA are important to consider when comparing performance results to improve future clinical applications. To this end, we prepared semi-interpenetrating polymer networks (semi-IPNs) of L-PRP and HA and characterized their polymerization kinetics, morphology, swelling ratio, stability and rheological behavior, which we found to be tunable according to the HA molar mass (MM). Mesenchymal stem cells derived from human adipose tissue (h-AdMSCs) seeded in the semi-IPNs had superior viability and chondrogenesis and osteogenesis capabilities compared to the viability and capabilities of fibrin. We have demonstrated that the preparation of the semi-IPNs under controlled mixing ensured the formation of cell-friendly hydrogels rich in soluble factors and with tunable properties according to the HA MM, rendering them suitable for clinical applications in regenerative medicine.

1. Introduction

Leukocyte- and platelet-rich plasma (L-PRP) consists of a concentrate of platelets, leukocytes, proteins and other components that after activation forms fibrin network, a matrix that acts as a reservoir of soluble factors that orchestrate healing mechanisms [1]. Platelets store many growth factors (GFs), chemokines and proteins in their alpha granules, as well as exosomes and microparticles that act as mediators in various physiological processes. Activated leukocytes secrete cytokines that, in addition to their inflammatory behavior, have important roles in maintaining homeostasis by stimulating cell activity [2–4]. Furthermore, the inflammatory phase is crucial for the healing process because it promotes remodeling and induces the tissue contraction phase. Finally, monocyte differentiation into macrophages during these immune response processes is of great importance due to macrophage plasticity into the M1 (inflammatory) and M2 (anti-inflammatory) phenotypes and its contribution to regeneration [5,6]. Therefore, both platelets and leukocytes are essential for global regenerative processes [7]. The effectiveness of locally injected L-PRP on tissue regeneration has been observed in clinical studies, particularly in the treatment of cartilage and bone diseases [8–10].

L-PRP efficacy can be potentially increased when it is combined with hyaluronic acid (HA) [11], a glycosaminoglycan present in the extracellular matrix (ECM) of joint tissues in the high molar mass (HMM) form (> 1000 kDa), where it contributes to the maintenance of tissue integrity by promoting its organization, elasticity, lubrication and shock absorption capacity [12,13]. In the organism, HMM HA is naturally degraded into smaller fragments that form oligosaccharides (< 20 disaccharides) and the HA of low (LMM) and intermediate molar mass (20 to 450 kDa) that have different biological properties, such as promoters of angiogenesis and as stimulators of inflammatory cytokine expression [10–12].

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ARTIGO

The Regenerative Medicine Potential of PRP in Elite Athlete Injuries

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- **José Fábio Santos Duarte Lana**
- Carolina Masini Pedrozo
- Ivan Corrêa Bottene
- Jose Renan Moyses De Medeiros
- Letícia Queiroz Da Silva

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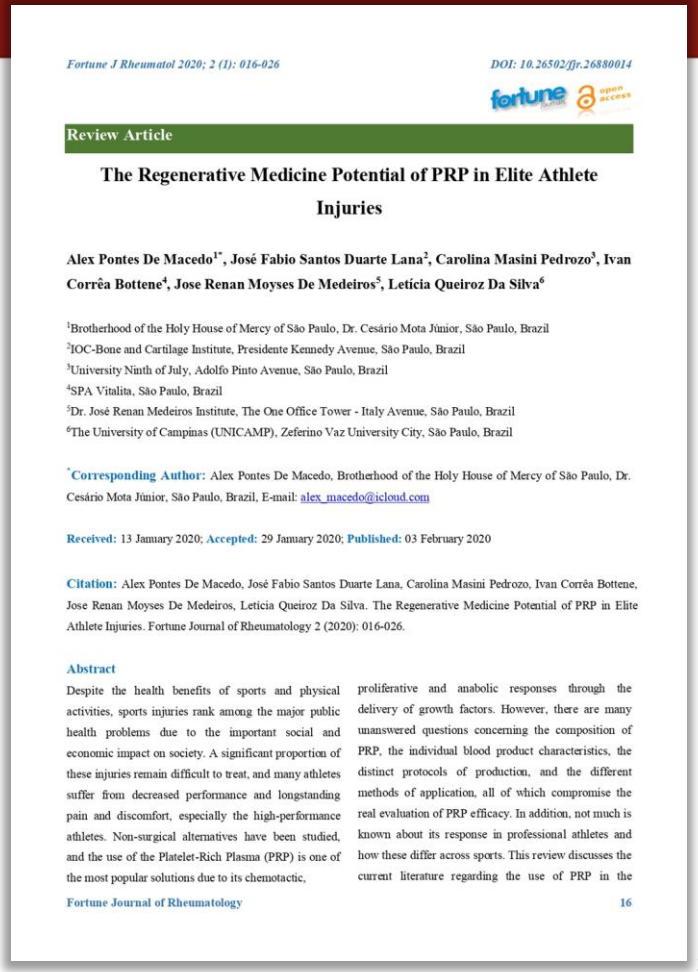

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Review Article

The Regenerative Medicine Potential of PRP in Elite Athlete Injuries

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Abstract

Despite the health benefits of sports and physical activities, sports injuries rank among the major public health problems due to the important social and economic impact on society. A significant proportion of these injuries remain difficult to treat, and many athletes suffer from decreased performance and longstanding pain and discomfort, especially the high-performance athletes. Non-surgical alternatives have been studied, and the use of the Platelet-Rich Plasma (PRP) is one of the most popular solutions due to its chemotactic, proliferative and anabolic responses through the delivery of growth factors. However, there are many unanswered questions concerning the composition of PRP, the individual blood product characteristics, the distinct protocols of production, and the different methods of application, all of which compromise the real evaluation of PRP efficacy. In addition, not much is known about its response in professional athletes and how these differ across sports. This review discusses the current literature regarding the use of PRP in the

ARTIGO

Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine

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- William Murrell
- Gabriel Silva Santos
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Review article

Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine

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ABSTRACT

Extracorporeal shockwave therapy (ESWT) is a popular non-invasive therapeutic modality in the medical field for the treatment of numerous musculoskeletal disorders. This technique first emerged around the 1980s as extracorporeal shockwave lithotripsy and has been studied since then for its application towards orthopedics and traumatology. ESWT works by the emission of acoustic waves (shockwaves) that carry energy and can propagate through tissues. Shockwaves can generate interstitial and extracellular responses, producing many beneficial effects such as: pain relief, vascularization, protein biosynthesis, cell proliferation, neuro and chondroprotection, and destruction of calcium deposits in musculoskeletal structures. The combination of these effects can lead to tissue regeneration and significant alleviation of pain, improving functional outcomes in injured tissue. Considering these facts, ESWT shows great potential as a useful regenerative medicine technique for the treatment of numerous musculoskeletal injuries.

1. Introduction

Extracorporeal shockwave therapy (ESWT) has become a popular non-invasive therapeutic modality in the field of orthopedics and traumatology for the treatment of many musculoskeletal disorders, including problematic soft tissue wounds. ESWT first emerged around the 1980s as extracorporeal shockwave lithotripsy (ESWL), a tool used to disintegrate renal stones.[1] The essential principle behind this technique revolves around the action of shockwaves, which are rapid but short duration acoustic waves that carry energy and can propagate through tissues.[2] In contrast to ESWL, the application of shockwaves in orthopedics (orthotripsy) can be beneficial due to their ability to cause interstitial and extracellular responses which lead to tissue regeneration.[3] In general, ESWT bears positive effects in the management of cartilage and bone diseases. This therapy has shown promising results in the treatment of various musculoskeletal disorders, including tendinitis, epicondylitis, plantar fasciitis, trocanteritis, and "jumper's knee", as examples.[3,4] Furthermore, its utility can also be applied towards the treatment of non-union in long bone fractures, avascular necrosis of the femoral head, chronic diabetic or non-diabetic ulcers, ischemic heart disease and even erectile dysfunction.[2,4] Acting as a mechanical stimulus, it is believed that ESWT promotes healing via mechanotransduction.[5] Reportedly, biological responses include tissue regeneration, wound healing, angiogenesis and bone remodeling.[5–9] Additionally, it may also alleviate pain by means of hyperstimulation analgesia.[10,11] Previous investigations have suggested that mechanotransduction seems to be the major mechanism whereby ESWT triggers angiogenic and tissue regeneration responses at cellular and molecular levels, generating beneficial therapeutic effects in clinical scenarios.[8,12] Although ESWT may be utilized to treat a variety of physical problems involving musculoskeletal tissues, there may be different

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ARTIGO

Bone marrow-derived products: A classification proposal – bone marrow aspirate, bone marrow aspirate concentrate or hybrid?

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REVIEW

Bone marrow-derived products: A classification proposal – bone marrow aspirate, bone marrow aspirate concentrate or hybrid?

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Author contributions: Purita J and Kolber M wrote the manuscript; Lana JFSD and Rodrigues BL designed the ACH classification concepts; Huber SC and Caliari-Oliveira C created Tables 1 and 2 and compiled the reference list; Santos GS proposed the schematic representation of the ACH classification illustrated in Figure 1 and Mosaner T reviewed the literature to validate information.

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Abstract

Degenerative musculoskeletal disorders are one of the top causes of pain and disability in the adult population. Current available alternatives to mitigate symptoms include conservative treatments such as the administration of pharmacological agents and an educative approach towards lifestyle modification. The use of certain analgesics, such as opiates and corticosteroids, delivers short term results but do not address the etiological source of pain and disability. Also, prolonged use of such medications may cause additional complications. Therefore, the demand for musculoskeletal tissue regeneration has led to an alternative approach referred to as "orthobiologics". This alternative is based on cellular and molecular components capable of inducing and promoting tissue repair. Bone marrow (BM) aspirate (BMA) and concentrate are well-known orthobiologics used to treat musculoskeletal conditions. Orthobiologics derived from the BM have been discussed in the literature; however, the lack of standardization regarding collection and processing protocols presents a challenge for generalization of study outcomes and determination of efficacy. Since BM-derived orthobiologics have not yet been classified, to our knowledge, this manuscript proposes the ACH classification system, which speaks to BMA (A), BMA and concentrate (C) and hybrid (H), which combines A and C. This classification proposes and describes 8 parameters that are relevant for the quality of biological products. The more parameters used would imply greater characterization and complexity of the evaluation of the biological product used.

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ARTIGO

Metabolic syndrome and subchondral bone alterations: The rise of osteoarthritis - A review

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- Gabriel Silva Santos
- Silvia Beatriz Coutinho Visoni
- Vitor Ohana Marques Azzini
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Metabolic syndrome and subchondral bone alterations: The rise of osteoarthritis – A review

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ABSTRACT

Metabolic syndrome (MS) has become one of the top major health burdens for over three decades not only due to its effects on cardiovascular health but also its implications in orthopedics. Extensive research has shown that MS is tightly linked to osteoarthritis and inflammation, a process which appears to primarily occur in the subchondral bone via the incidence of bone-marrow lesions (BMLs). Numerous studies identify obesity, dyslipidemia, insulin resistance and hypertension as the top metabolic risk factors, the so-called "deadly quartet". These factors are responsible for the disruptive physiological processes that culminate in detrimental alterations within the subchondral bone, cartilage damage and, overall, the predominant pro-inflammatory joint microenvironment. Although it has long been thought that osteoarthritis was limited to the cartilage component of the joint, other studies indicate that the disease may originate from the harmful alterations that occur primarily in the subchondral bone, especially via means of vascular pathology. Since metabolic risk factors are manageable to a certain extent, it is therefore possible to decelerate the progression of OA and mitigate its devastating effects on the subchondral bone and subsequent articular cartilage damage.

Methods: Literature was reviewed using PubMed and Google Scholar in order to find a correlation between metabolic syndrome and osteoarthritic progression. The investigation included a combination of nomenclature such as: "metabolic syndrome", "obesity", "insulin resistance", "hypertension", "dyslipidemia", "low-grade systemic inflammation", "osteoarthritis", "subchondral bone", "cartilage" and "inflammatory biomarkers".

Conclusion: Based on several studies, there seems to be a significant association between The Deadly Quartet (metabolic syndrome), dysregulation of both pro- and anti-inflammatory biomarkers, and osteoarthritic progression arising from unbridled systemic inflammation.

1. Introduction

Metabolic syndrome is a major health condition that continues to escalate and challenge public and clinical health on a global scale as a result of urbanization, increased calorie intake, increasing obesity and sedentary life habits.[1] This is a complex condition which is tightly connected to multiple biochemical and physiological pathways, often directly associated with the development of

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ARTIGO

Bone marrow aspirate clot: A feasible orthobiologic

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Bone marrow aspirate clot: A feasible orthobiologic

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ABSTRACT

Musculoskeletal disorders are one of the major health burdens and a leading source of disability worldwide, affecting both juvenile and elderly populations either as a consequence of ageing or extrinsic factors such as physical injuries. This condition often involves a group of locomotor structures such as the bones, joints and muscles and may therefore cause significant economic and emotional impact.

Some pharmacological and non-pharmacological treatments have been considered as potential solutions, however, these alternatives have provided quite limited efficacy due to the short-term effect on pain management and inability to restore damaged tissue.

The emergence of novel therapeutic alternatives such as the application of orthobiologics, particularly bone marrow aspirate (BMA) clot, have bestowed medical experts with considerable optimism as evidenced by the significant results found in numerous studies addressed in this manuscript. Although other products have been proposed for the treatment of musculoskeletal injuries, the peculiar interest in BMA, fibrin clot and associated fibrinolytic mechanisms continues to expand.

BMA is a rich source of various cellular and molecular components which have demonstrated positive effects on tissue regeneration in many *in vitro* and *in vivo* models of musculoskeletal injuries. In addition to being able to undergo self-renewal and differentiation, the hematopoietic and mesenchymal stem cells present in this orthobiologic elicit key immunomodulatory and paracrine roles in inflammatory responses in tissue injury and drive the coagulation cascade towards tissue repair via different mechanisms.

Although promising, these complex regenerative mechanisms have not yet been fully elucidated.

1. Introduction

Musculoskeletal disorders are one of the major contributors to disability worldwide. According to the World Health Organization, the global burden of musculoskeletal disease was the highest contributor to global disability in 2017.[1] Most of the musculoskeletal degenerative conditions are not exclusive to elderly people since young individuals can also be affected by sports injuries. Those conditions may affect bones, joints, and muscles and result in a great economic impact, limiting mobility and causing early retirement and reduced ability to participate in social activities.

Nowadays, the therapies available to treat those conditions comprise non-pharmacological treatments (e.g. manual and

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ARTIGO

The protective role of glutathione in osteoarthritis

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- Marco Antonio Percope Andrade
- **José Fábio Santos Duarte Lana**

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The protective role of glutathione in osteoarthritis

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ABSTRACT

It is currently understood that osteoarthritis (OA) is a major chronic inflammatory musculoskeletal disease. While this disease has long been attributed to biomechanical trauma, recent evidence establishes a significant correlation between osteoarthritic progression and unbridled oxidative stress, responsible for prolonged inflammation. Research describes this as a disturbance in the balanced production of reactive oxygen species (ROS) and antioxidant defenses, generating macromolecular damage and disrupted redox signaling and control. Since ROS pathways are being considered new targets for OA treatment, the development of antioxidant therapy to counteract exacerbated oxidative stress is being continuously researched and enhanced in order to fortify the cellular defenses. Experiments with glutathione and its precursor molecule, *N*-acetylcysteine (NAC), have shown interesting results in the literature for the management of OA, where they have demonstrated efficacy in reducing cartilage degradation and inflammation markers as well as significant improvements in pain and functional outcomes. Glutathione remains a safe, effective and overall cheap treatment alternative in comparison to other current therapeutic solutions and, for these reasons, it may prove to be comparably superior under particular circumstances.
Methods: Literature was reviewed using PubMed and Google Scholar in order to bring up significant evidence and illustrate the defensive mechanisms of antioxidant compounds against oxidative damage in the onset of musculoskeletal diseases. The investigation included a combination of keywords such as: oxidative stress, oxidative damage, inflammation, osteoarthritis, antioxidant, glutathione, *n*-acetylcysteine, redox, and cell signaling.
Conclusion: Based on the numerous studies included in this literature review, glutathione and its precursor *N*-acetylcysteine have demonstrated significant protective effects in events of prolonged, exacerbated oxidative stress as seen in chronic inflammatory musculoskeletal disorders such as osteoarthritis.

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1. Introduction

Osteoarthritis (OA) is a major painful chronic joint disease affecting various anatomical sites including the hip, knee and hand, being responsible for loss of function and disability in adults.[1,2] This complex multifactorial orthopedic condition, commonly attributed to aging and obesity, is known to affect more than one-third of the

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ARTIGO

Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020

- Peter Everts
- Kentaro Onishi
- Prathap Jayaram
- **José Fábio Lana**
- Kenneth Mautner

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International Journal of *Molecular Sciences*

MDPI

Review

Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020

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check for updates

Abstract: Emerging autologous cellular therapies that utilize platelet-rich plasma (PRP) applications have the potential to play adjunctive roles in a variety of regenerative medicine treatment plans. There is a global unmet need for tissue repair strategies to treat musculoskeletal (MSK) and spinal disorders, osteoarthritis (OA), and patients with chronic complex and recalcitrant wounds. PRP therapy is based on the fact that platelet growth factors (PGFs) support the three phases of wound healing and repair cascade (inflammation, proliferation, remodeling). Many different PRP formulations have been evaluated, originating from human, in vitro, and animal studies. However, recommendations from in vitro and animal research often lead to different clinical outcomes because it is difficult to translate non-clinical study outcomes and methodology recommendations to human clinical treatment protocols. In recent years, progress has been made in understanding PRP technology and the concepts for bioformulation, and new research directives and new indications have been suggested. In this review, we will discuss recent developments regarding PRP preparation and composition regarding platelet dosing, leukocyte activities concerning innate and adaptive immunomodulation, serotonin (5-HT) effects, and pain killing. Furthermore, we discuss PRP mechanisms related to inflammation and angiogenesis in tissue repair and regenerative processes. Lastly, we will review the effect of certain drugs on PRP activity, and the combination of PRP and rehabilitation protocols.

Keywords: platelet-rich plasma; regenerative medicine; platelet dosing; neutrophils; monocytes; lymphocytes; inflammation; angiogenesis; serotonin; analgesic effects; immunomodulation; rehabilitation

1. Introduction

Autologous platelet-rich plasma (PRP) is the processed liquid fraction of autologous peripheral blood with a platelet concentration above the baseline [1]. PRP therapies have been used for various indications for more than 30 years, resulting in considerable interest in the potential of autologous PRP in regenerative medicine. The term orthobiologics has recently been introduced for the treatment of musculoskeletal (MSK) disorders, with promising results for the regenerative capacity of the heterogeneous biological active PRP cellular cocktail. Currently, PRP therapies are suitable treatment options with clinical benefits, with encouraging patient outcomes reported [2–4]. However,

ARTIGO

Preparing the Soil: Targeting Meta-Inflammation in Musculoskeletal Regenerative Medicine

- Alberto Gobbi
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- **José Fábio Santos Duarte Lana**
- Gabriel Azzini

Publicação: 2021
Veículo: ISAKOS - Global Link

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CURRENT CONCEPTS

Preparing the Soil: Targeting Meta-Inflammation in Musculoskeletal Regenerative Medicine

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Introduction

It is well known that the rise in metabolic syndrome (MS) has become a major health burden across the globe. Excessive caloric intake and poor dietary habits pave the way for the progression of "meta-inflammation," which disrupts metabolic equilibrium and eventually aggravates low-grade chronic inflammation throughout the body[1].

By definition, meta-inflammation is a state of chronic inflammation mediated by macrophages that are present in certain locations such as the liver, muscle, adipose tissue, pancreas, colon, and brain[2]. These cells are known to coordinate immune activity and homeostasis, taking on different roles and displaying many cellular properties, depending on time and various biochemical stimuli[2]. Meta-inflammation can disrupt proper cell signaling and macrophage polarization, a process that also appears to be linked to MS. While meta-inflammation and disrupted cell signaling have been associated with MS and other autoimmune disorders, other unknowns still remain to be explored with regard to the origins and initiatory mechanisms of this disorder. In any case, this disorder still poses a great challenge for orthopaedic surgeons and other medical practitioners as chronic inflammation has been shown to harm musculoskeletal structures[1]. Musculoskeletal complications may be treated with conservative alternatives as well as novel therapeutic interventions such as the application of orthobiologics, which are regenerative therapies that are used to facilitate the healing of variety of tissues. Popular examples include hyaluronic acid, platelet-rich plasma, bone marrow, adipose tissue, and expanded mesenchymal stem cells[3]. In order to promote a more effective response, however, medical professionals must "prepare the soil" before managing a patient with an orthobiologic intervention. In other words, the target tissue must be biologically receptive to therapeutic agents. This goal can be achieved by designing health protocols that modulate an individual's metabolic profile with the inclusion of dietary modifications, intermittent fasting, health supplements (minerals and vitamins), hormonal regulation, and other alternatives.

The objective of this review is to discuss some but not all of the known biologic soil-preparation alternatives in the fight against meta-inflammation, demonstrating the importance of primarily addressing low-grade chronic inflammation preceding interventional therapies.

Macrophage Polarization

The polarization of macrophages has been broadly divided into two distinct phenotypes (M1 and M2), which are attributed to the corresponding Th1 and Th2 (t helper) cell responses[4]. The M1 macrophages have been classically associated with inflammatory responses. These responses are usually mediated by certain inflammatory agents such as interferon-γ (IFN-γ) and lipopolysaccharide (LPS), which allows these cells to develop microbicidal and proinflammatory properties, a main feature of this specific phenotype. M1 receptors for cytokines and LPS, in turn, allow signal transduction, which results in the expression of well-known inflammatory mediators such as inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), and chemokine (C-C motif) ligand 2 (CCL2/MCP-1)[4].

ARTIGO

The role of Glutathione as an adjunct therapy in the treatment of patients with COVID-19-Related Acute Respiratory Syndrome

- Taís Mazzini Setti
- Thiago Setti
- Lucas Furtado da Fonseca
- Stephany Cares Huber
- Gabriel Silva Santos
- **José Fábio Santos Duarte Lana**

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Research Article,

The role of Glutathione as an adjunct therapy in the treatment of patients with COVID-19-Related Acute Respiratory Syndrome

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Abstract:

Covid-19 is a novel coronavirus disease that has been (SARS-CoV-2) responsible for a worldwide pandemic of infectious pneumonia associated with severe acute respiratory syndrome. Although in most cases the disease can be resolved on its own, in severe or critical cases, patients can ultimately pass away, mainly due to the diffuse and massive alveolar damage associated with disease progression. One in four patients will be admitted to the Intensive Care Unit (ICU). A constant characteristic in severely affected patients is the exacerbated systemic inflammatory response. This is attributed to the excessive immune response mediated by cytokine secretion, which therefore causes acute lung injury, acute respiratory distress syndrome, multiple organ failure and even death. Currently, there are no effective antiviral agents and there are no fully elucidated or validated therapeutic options that can halt disease progression in some patients. Therefore, there is an urgent need for new treatments to delay the excessive inflammatory response and accelerate the repair of functional lung tissue in these patients. Glutathione may fit these criteria because it has some properties which can be associated with antiviral effects and it also participates in immune responses with the ability to balance oxidative stress.

Key words: acute respiratory syndrome, COVID-19, glutathione.

ARTIGO

Platelet-rich plasma vs bone marrow aspirate concentrate: An overview of mechanisms of action and orthobiologic synergistic effects

- José Fábio Santos Duarte Lana
- Lucas Furtado da Fonseca
- Rafael da Rocha Macedo
- Tomas Mosaner
- William Murrell
- Ashok Kumar
- Joseph Purita
- Marco Antonio Percope de Andrade

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DOI: 10.4252/wjsc.v13.i2.155 ISSN 1948-0210 (online)

MINIREVIEWS

Platelet-rich plasma *vs* bone marrow aspirate concentrate: An overview of mechanisms of action and orthobiologic synergistic effects

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Author contributions: Purita J wrote the manuscript; de Andrade MAP proposed the research subtopics; Kumar A was responsible for navigating the literature and sharing the relevant studies that were included in this review; Murrell W and da Fonseca LF shared significant knowledge regarding the use of orthobiologics in regenerative medicine; Mosaner T formatted the citations and compiled the references; Macedo RR revised and formatted the body of the manuscript and verified spelling, punctuation and grammatical errors; Lana JFSD was responsible for reviewing and approving all the modifications made to the manuscript from draft to final version.

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

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Abstract

The use of orthobiologics as a novel therapy for the treatment of numerous musculoskeletal disorders has increased considerably over the past decade. Currently, there are multiple alternatives available as suitable treatments; however, the use of autologous blood-derived products such as platelet-rich plasma (PRP), bone marrow aspirate (BMA) and BMA concentrate (BMAC), specifically, is expanding. Although many investigations attempted to demonstrate the effectiveness of these therapies, even with positive results, the literature lacks standardized protocols and overall accuracy in study designs, which leads to variance and difficulty in reproducibility of protocols. The efficacy of PRP for the treatment of cartilage, bone and muscle tissues is well known.

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ARTIGO

Biofat grafts as an orthobiologic tool in osteoarthritis: An update and classification proposal

- Rafael da Rocha Macedo
- Lucas Furtado da Fonseca
- **José Fábio Santos Duarte Lana**
- Tomas Mosaner
- Joseph Purita
- MAP de Andrade
- Luciano Miller Rodrigues
- Patricio Centurion

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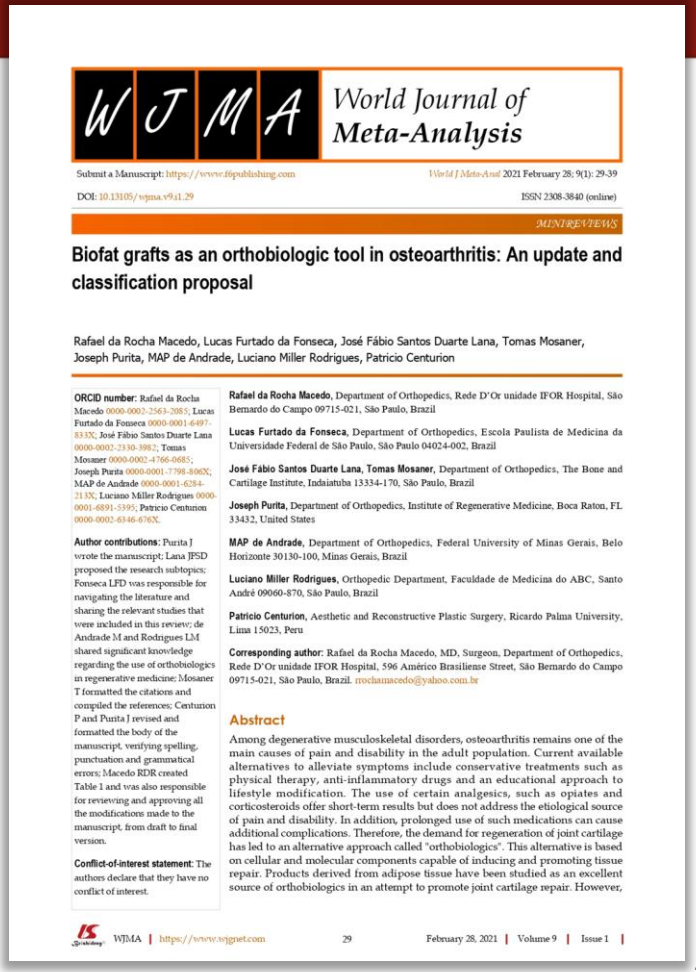

World Journal of Meta-Analysis

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MINIREVIEWS

Biofat grafts as an orthobiologic tool in osteoarthritis: An update and classification proposal

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Abstract

Among degenerative musculoskeletal disorders, osteoarthritis remains one of the main causes of pain and disability in the adult population. Current available alternatives to alleviate symptoms include conservative treatments such as physical therapy, anti-inflammatory drugs and an educational approach to lifestyle modification. The use of certain analgesics, such as opiates and corticosteroids offer short-term results but does not address the etiological source of pain and disability. In addition, prolonged use of such medications can cause additional complications. Therefore, the demand for regeneration of joint cartilage has led to an alternative approach called "orthobiologics". This alternative is based on cellular and molecular components capable of inducing and promoting tissue repair. Products derived from adipose tissue have been studied as an excellent source of orthobiologics in an attempt to promote joint cartilage repair. However,

Author contributions: Purita J wrote the manuscript; Lana JFSD proposed the research subtopics; Fonseca LFD was responsible for navigating the literature and sharing the relevant studies that were included in this review; de Andrade M and Rodrigues LM shared significant knowledge regarding the use of orthobiologics in regenerative medicine; Mosaner T formatted the citations and compiled the references; Centurion P and Purita J revised and formatted the body of the manuscript, verifying spelling, punctuation and grammatical errors; Macedo RDR created Table 1 and was also responsible for reviewing and approving all the modifications made to the manuscript, from draft to final version.

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

ARTIGO

Bone Marrow Aspirate Matrix: A Convenient Ally in Regenerative Medicine

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- Alberto Gobbi
- Joseph Purita
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Pesquisa completa aqui!

International Journal of Molecular Sciences

MDPI

Review

Bone Marrow Aspirate Matrix: A Convenient Ally in Regenerative Medicine

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Abstract: The rise in musculoskeletal disorders has prompted medical experts to devise novel effective alternatives to treat complicated orthopedic conditions. The ever-expanding field of regenerative medicine has allowed researchers to appreciate the therapeutic value of bone marrow-derived biological products, such as the bone marrow aspirate (BMA) clot, a potent orthobiologic which has often been dismissed and regarded as a technical complication. Numerous in vitro and in vivo studies have contributed to the expansion of medical knowledge, revealing optimistic results concerning the application of autologous bone marrow towards various impactful disorders. The bone marrow accommodates a diverse family of cell populations and a rich secretome; therefore, autologous BMA-derived products such as the "BMA Matrix", may represent a safe and viable approach, able to reduce the costs and some drawbacks linked to the expansion of bone marrow. BMA provides —it eliminates many hurdles associated with its preparation, especially in regards to regulatory compliance. The BMA Matrix represents a suitable alternative, indicated for the enhancement of tissue repair mechanisms by modulating inflammation and acting as a natural biological scaffold as well as a reservoir of cytokines and growth factors that support cell activity. Although promising, more clinical studies are warranted in order to further clarify the efficacy of this strategy.

Keywords: tissue healing; bone marrow aspirate clot; fibrin matrix; hyaluronic acid; regenerative medicine; orthobiologics

1. Introduction

The rise in musculoskeletal disorders has been a great cause of concern in recent decades. Major health organizations such as the World Health Organization (WHO) confirm that musculoskeletal diseases are the highest contributor to global disability [1]. These health conditions can affect both young and elderly populations by putting bones, joint and muscle tissues at risk and generating a detrimental socioeconomic and psychosocial impact. Current interventional strategies are divided into pharmacological and nonpharmacological alternatives. Popular nonpharmacological strategies usually employ exercise,

ARTIGO

Orthobiologics in the treatment of hip disorders

- André Vinícius Saueressig Kruel
- Lucas Leite Ribeiro
- Paulo David Gusmão
- Stephany Cares Huber
- **José Fábio Santos Duarte Lana**

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MINIREVIEWS

Orthobiologics in the treatment of hip disorders

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Author contributions: All authors contributed to the study conception and design. The body of the manuscript was written by Kruel A; Literature research was conducted by Ribeiro LL; Gusmão PD revised the draft and made suggestions for improvement; Huber SC formatted the manuscript and made all the necessary adjustments in order to prepare the manuscript for the submission process; Lana JFSD acted as the group leader, designing the main concepts and subtopics of discussion presented in the manuscript, critically revising both the initial and final versions of the manuscript before submission.

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

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Abstract

Orthobiologics are biological materials that are intended for the regeneration or healing of bone, cartilage and soft tissues. In this review we discuss the use of orthobiologics for hip disorders providing an update. The orthobiologics included in this article are hyaluronic acid, platelet rich plasma, bone marrow, adipose tissue and expanded mesenchymal stem cells. We explain the concepts and definitions of each orthobiological product, and the literature regarding its use in the hip joint. The paucity of guidelines for the production and characterization of the biological products leads to uneven results across the literature. Each biologic therapy has indications and benefits; however, noteworthy are the characterization of the orthobiologics, the application method and outcome analysis for further improvement of each technique.

Key Words: Orthobiologics; Hip disorders; Platelet-rich plasma; Mesenchymal stem cells; Bone marrow; Adipose tissue

ARTIGO

The regenerative mechanisms of platelet-rich plasma: A review

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- Tania Liana Chiesa
- Gabriel Ohana Azzini
- Lucas Furtado da Fonseca
- Antonio Fernando dos Santos
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- **José Fábio Lana**

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Review article

The regenerative mechanisms of platelet-rich plasma: A review

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Inflammation

ABSTRACT

Orthobiologics continue to gain popularity in many areas of medical science, especially in the field of regenerative medicine. Platelet-rich plasma derivatives are orthobiologic tools of particular interest. These biologic products can be obtained via centrifugation of a patient's whole blood and the components can then be subsequently isolated, concentrated and ultimately administered into injured tissues, particularly in areas where standard healing is disrupted. The elevated concentration of platelets above the basal value enables accelerated growth of various tissues with minimal side effects. The application of autologous orthobiologics is a relatively new biotechnology undergoing expansion which continues to reveal optimistic results in the stimulation and enhanced healing of various sorts of tissue injuries. The local release of growth factors and cytokines contained in platelet alpha granules accelerates and ameliorates tissue repair processes, mimicking and supporting standard wound healing. This effect is greatly enhanced upon combination with the fibrinolytic system, which are essential for complete regeneration. Fibrinolytic reactions can dictate proper cellular recruitment of certain cell populations such as mesenchymal stem cells and other immunomodulatory agents. Additionally, these reactions also control proteolytic activity in areas of wound healing and regenerative processes of mesodermal tissues including bone, cartilage, and muscle, which makes it particularly valuable for musculoskeletal health, for instance. Although many investigations have demonstrated significant results with platelet-rich plasma derivatives, further studies are still warranted.

1. Introduction

The use of autologous hematological components has become a highly attractive therapeutic tool in many areas of medical science for the treatment of various debilitations. Platelet-rich plasma (PRP), for example, is a popular treatment modality and has raised a significant level of attention amongst medical professionals over the last two decades. This is mainly attributed to the promising potential of PRP in enhancing regenerative processes, which has long been appreciated by oral and maxillofacial surgeons, veterinarians, dermatologists and sports medicine experts [1,2].

Platelet-rich plasma can be generated by the centrifugation of an individual's whole blood, carrying a variety of cells with a primary focus on concentrated platelets above baseline [3,4], as Fig. 1 illustrates.

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ARTIGO

Human platelet lysate - A potent (and overlooked) orthobiologic

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- Stephany Cares Huber
- Taís Mazzini Setti
- Thiago Setti
- **José Fábio Lana**

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Review article

Human platelet lysate – A potent (and overlooked) orthobiologic

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ABSTRACT

The knowledge of the essential role of platelets in tissue healing is gradually increasing and as regenerative medicine prompts new solutions, platelet-derived bioproducts have been proposed as a potential tool in this field. In orthopaedics and sports medicine, the use of PRP has been rapidly increasing in popularity as patients seek novel non-surgical approaches to acute and chronic musculoskeletal conditions. The concept of having platelets as a secretory organ other than a mere sponge-like coagulation component opens up new frontiers for the use of the platelet secretome. Platelet lysate is a solution saturated by growth factors, proteins, cytokines, and chemokines involved in crucial healing processes and is administered to treat different diseases such as alopecia, oral mucositis, radicular pain, osteoarthritis, and cartilage and tendon disorders. For this purpose, the abundant presence of growth factors and chemokines stored in platelet granules can be naturally released by different strategies, mostly through lyophilization, thrombin activation or ultrasound baths (ultrasonication). As a result, human platelet lysate can be produced and applied as a pure orthobiologic. This review outlines the current knowledge about human platelet lysate as a powerful adjuvant in the orthobiological use for the treatment of musculoskeletal injuries, without however failing to raise some of its most applicable basic science.

1. Introduction

The increasing use of orthobiologics in musculoskeletal injuries, especially cell-based therapies involving mesenchymal stem cells (MSCs), has led to an increasing demand for clarification (or elucidation) of the role of blood components. Platelets play an essential role not only in primary hemostasis but also in wound healing and tissue regeneration.[1] Significant knowledge about platelet biology has been gained during the last decades with increased focus on their regenerative properties. Indeed, platelets behave as a natural reservoir with secretion capacity that is now observed through many studies in the literature.[2,3] In this context, platelet-rich plasma (PRP) appears to be the most popular platelet-derived product, which represents a biological treatment for various musculoskeletal injuries involving tendons, ligaments, cartilage and bone. PRP is one of the many new developments within the expanding field of regenerative medicine. Although different formulations have been described, it aims to improve the process of tissue repair through local delivery of autologous bioactive agents to influence critical physiological mechanisms such as inflammation, angiogenesis or extracellular matrix (ECM) synthesis.[4] Recently, Lana et al. proposed a new classification for PRP in order to standardize PRP procedures.[5] Criteria included harvest method, activation, red blood cells, number of spins, image guidance, leukocytes number and light activation in order to propose a consensus for new studies. To be defined as a "working PRP", the platelet concentration should be around 10^6 per microliter, since higher concentrations have not shown enhancements tissue healing.[6] Platelet-rich plasma (PRP) is also defined as platelets concentrated over the basal number (four-to nine-fold) in a small plasma volume.

By its secretome, platelets have a central role in hemostasis, secreting a cargo of proteins that are found in alpha granules, dense

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ARTIGO

Nebulization of glutathione and N-Acetylcysteine as an adjuvant therapy for COVID-19 onset

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- Anna Vitória Santos Duarte Lana
- Quézia Souza Rodrigues
- Gabriel Silva Santos
- Riya Navani
- Annu Navani
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- Tomas Mosaner
- Claudio Lopes Simplicio
- Taís Mazzini Setti

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Review Paper

Nebulization of glutathione and N-Acetylcysteine as an adjuvant therapy for COVID-19 onset

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ABSTRACT

Ever since its emergence, the highly transmissible and debilitating coronavirus disease spread at an incredibly fast rate, causing global devastation in a matter of months. SARS-CoV-2, the novel coronavirus responsible for COVID-19, infects hosts after binding to ACE2 receptors present on cells from many structures pertaining to the respiratory, cardiac, hematological, neurological, renal and gastrointestinal systems. COVID-19, however, appears to trigger a severe cytokine storm syndrome in pulmonary structures, resulting in oxidative stress, exacerbated inflammation and alveolar injury. Due to the recent nature of this disease no treatments have shown complete efficacy and safety. More recently, however, researchers have begun to direct some attention towards GSH and NAC. These natural antioxidants play an essential role in several biological processes in the body, especially the maintenance of the redox equilibrium. In fact, many diseases appear to be strongly related to severe oxidative stress and deficiency of endogenous GSH. The high ratios of ROS over GSH, in particular, appear to reflect severity of symptoms and prolonged hospitalization of COVID-19 patients. This imbalance interferes with the body's ability to detoxify the cellular microenvironment, fold proteins, replenish antioxidant levels, maintain healthy immune responses and even modulate apoptotic events. Oral administration of GSH and NAC is convenient and safe, but they are susceptible to degradation in the digestive tract. Considering this drawback, nebulization of GSH and NAC as an adjuvant therapy may therefore be a viable alternative for the management of the early stages of COVID-19.

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ARTIGO

Characterization of autologous platelet rich plasma (PRP) and its biological effects in patients with Behçet's Disease

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- Silmara Aparecida de Lima Montalvao
- Zoraida Sachetto
- **Jose Fabio Santos Duarte Lana**
- Joyce Maria Annichino-Bizzacchi

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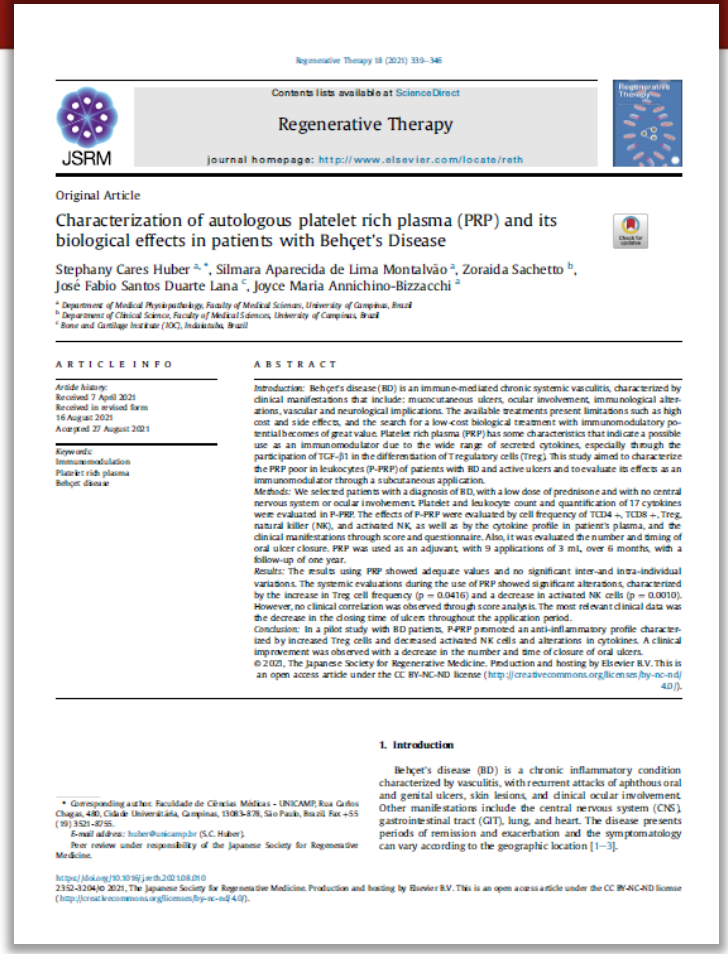

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JSRM

Original Article

Characterization of autologous platelet rich plasma (PRP) and its biological effects in patients with Behçet's Disease

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ABSTRACT

Introduction: Behçet's disease (BD) is an immune-mediated chronic systemic vasculitis, characterized by clinical manifestations that include: mucocutaneous ulcers, ocular involvement, immunological alterations, vascular and neurological implications. The available treatments present limitations such as high cost and side effects, and the search for a low-cost biological treatment with immunomodulatory potential becomes of great value. Platelet rich plasma (PRP) has some characteristics that indicate a possible use as an immunomodulator due to the wide range of secreted cytokines, especially through the participation of TGF-β1 in the differentiation of T regulatory cells (Treg). This study aimed to characterize the PRP poor in leukocytes (P-PRP) of patients with BD and active ulcers and to evaluate its effects as an immunomodulator through a subcutaneous application.
Methods: We selected patients with a diagnosis of BD, with a low dose of prednisone and with no central nervous system or ocular involvement. Platelet and leukocyte count and quantification of 17 cytokines were evaluated in P-PRP. The effects of P-PRP were evaluated by cell frequency of TCD4 +, TCD8 +, Treg, natural killer (NK), and activated NK, as well as by the cytokine profile in patient's plasma, and the clinical manifestations through score and questionnaire. Also, it was evaluated the number and timing of oral ulcer closure. PRP was used as an adjuvant, with 9 applications of 3 mL, over 6 months, with a follow-up of one year.
Results: The results using PRP showed adequate values and no significant inter-and intra-individual variations. The systemic evaluations during the use of PRP showed significant alterations, characterized by the increase in Treg cell frequency ($p = 0.0416$) and a decrease in activated NK cells ($p = 0.0010$). However, no clinical correlation was observed through score analysis. The most relevant clinical data was the decrease in the closing time of ulcers throughout the application period.
Conclusion: In a pilot study with BD patients, P-PRP promoted an anti-inflammatory profile characterized by increased Treg cells and decreased activated NK cells and alterations in cytokines. A clinical improvement was observed with a decrease in the number and time of closure of oral ulcers.

1. Introduction

Behçet's disease (BD) is a chronic inflammatory condition characterized by vasculitis, with recurrent attacks of aphthous oral and genital ulcers, skin lesions, and clinical ocular involvement. Other manifestations include the central nervous system (CNS), gastrointestinal tract (GIT), lung, and heart. The disease presents periods of remission and exacerbation and the symptomatology can vary according to the geographic location [1–3].

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ARTIGO

Bone Marrow Aspirate for Delayed Union due to Severe Thoracic Rib Trauma

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- Thiago Setti
- Gabriel Silva Santos
- **José Fábio Lana**

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HSOA Journal of
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Case Report

Bone Marrow Aspirate for Delayed Union due to Severe Thoracic Rib Trauma

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Abstract

Study Design: Case report

Objectives: The objective is report a case of delayed union due to severe thoracic rib trauma involving multiple fractures by evaluation, interventional strategy and follow-up.

Background: Delayed union due to severe trauma is an impactful condition responsible for progressive deformity and pain where surgical intervention may still prove to be challenging in terms of success rates. Rib fracture is the most common form of blunt thoracic injury, affecting multiple costal structures in all types of thoracic trauma. Typical conservative treatments are usually limited to brace application and only for the control of pain in acute circumstances. Rib fracture is still an important communicator of trauma severity, as morbidity and mortality can increase according to the number of fractured ribs.

Materials and Methods: Computed tomography (CT) of the costal arches was performed in both diagnosis and follow-up. The patient received Bone Marrow Aspirate (BMA) infiltration treatment to treat the delayed union of fractured bones.

Results: All of the fractured ribs (from the 2nd to the 12th) with multiple affected regions were apparently consolidated. The bone overlaps on the 5th, 6th, 7th, 8th, 9th and 10th ribs, were also consolidated. There was no evidence of chest wall collapse or instability, and there was no evidence of anomalous joints or even pseudoarthrosis. The sternum showed no evidence of abnormalities. Patient exhibited significant pain improvement with BMA treatment.

Conclusion: In this peculiar setting, the infiltrations with BMA proved to be an efficient alternative tool for the treatment of severe thoracic rib trauma and delayed union. The patient returned with no complaints and CT evidence indicated that all of the fractured ribs had complete consolidation. Pain and functional outcome of the chest wall in terms of stability improved with the help of this orthobiologic alternative.

Keywords: Bone marrow aspirate; Delayed union; Fracture; Orthobiologics; Thoracic trauma

Key Points

- A 48-year-old man with a history of epilepsy fell off the roof of his house and suffered severe thoracic trauma, multiple rib fractures on the right rib cage, from the 2nd to the 12th ribs, affecting multiple points in the same costal arch.
- The condition was also associated with hemopneumothorax and unstable chest, as of September 2019. Signs of pain were detected in the right hemithorax. After 3 months, with no sign of consolidation of these fractures (Figure 1) a conclusion was found, characterizing it as possible pseudoarthrosis.
- The patient was submitted to two sessions of BMA injections for the management of delayed union. The first session occurred in February 2020, and the second one in June 2020.
- Delayed union was significantly improved with just two sessions with BMA administration. Three months after the first infiltration procedure the patient returned to the office and showed expressive improvements in pain and significant consolidation of fractured areas.

Introduction

The ribs are vital structures of the thoracic cage. Rib trauma can affect the lungs, mediastinum and other thoracoabdominal structures that rely on the integrity of the ribs for adequate protection [1]. Thoracic traumas usually arise from blunt or penetrating forces and can be broadly classified as chest wall, pulmonary or cardiovascular injury. Rib fractures are the most common form of blunt thoracic injuries affecting multiple points of these structures in all types of thoracic trauma [2]. Depending on the severity of traumatic rib injuries, key complications can encompass acute pain, hemothorax, pneumothorax, extrapleural hematoma, acute vascular injury and pulmonary

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ARTIGO

The Association between Gut Microbiota and Osteoarthritis: Does the Disease Begin in the Gut?

- Luciano C. Ramires
- Gabriel Silva Santos
- Rafaela Pereira Ramires
- Lucas Furtado da Fonseca
- Madhan Jeyaraman
- Sathish Muthu
- Anna Vitória Lana
- Gabriel Azzini
- Curtis Scott Smith
- **José Fábio Lana**

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International Journal of *Molecular Sciences*

MDPI

Review

The Association between Gut Microbiota and Osteoarthritis: Does the Disease Begin in the Gut?

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Abstract: Some say that all diseases begin in the gut. Interestingly, this concept is actually quite old, since it is attributed to the Ancient Greek physician Hippocrates, who proposed the hypothesis nearly 2500 years ago. The continuous breakthroughs in modern medicine have transformed our classic understanding of the gastrointestinal tract (GIT) and human health. Although the gut microbiota (GMB) has proven to be a core component of human health under standard metabolic conditions, there is now also a strong link connecting the composition and function of the GMB to the development of numerous diseases, especially the ones of musculoskeletal nature. The symbiotic microbes that reside in the gastrointestinal tract are very sensitive to biochemical stimuli and may respond in many different ways depending on the nature of these biological signals. Certain variables such as nutrition and physical modulation can either enhance or disrupt the equilibrium between the various species of gut microbes. In fact, fat-rich diets can cause dysbiosis, which decreases the number of protective bacteria and compromises the integrity of the epithelial barrier in the GIT. Overgrowth of pathogenic microbes then release higher quantities of toxic metabolites into the circulatory system, especially the pro-inflammatory cytokines detected in osteoarthritis (OA), thereby promoting inflammation and the initiation of many disease processes throughout the body. Although many studies link OA with GMB perturbations, further research is still needed.

Keywords: osteoarthritis; gut microbiota; metabolic syndrome; systemic inflammation

1. Introduction

Osteoarthritis (OA) has long been considered a degenerative disease that affects the hyaline cartilage alone. This orthopedic disorder still remains one of the most common degenerative and progressive joint diseases and a major cause of pain and disability in adults, affecting approximately 7% of the global population [1]. The Global Burden of Disease (GBD) 2019 study results revealed that the number of individuals affected by this

ARTIGO

Application of Orthobiologics in Achilles Tendinopathy: A Review

- Luciano C. Ramires
- Madhan Jeyaraman
- Sathish Muthu
- Navaladi Shankar
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- **José Fábio Lana**
- Ramya Lakshmi Rajendran
- Prakash Gangadaran
- Manasi P. Jogalekar
- Alfredo A. Cardoso
- Alex Eickhoff

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Review

Application of Orthobiologics in Achilles Tendinopathy: A Review

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Abstract: Orthobiologics are biological materials that are intended for the regeneration of bone, cartilage, and soft tissues. In this review, we discuss the application of orthobiologics in Achilles tendinopathy, more specifically. We explain the concepts and definitions of each orthobiologic and the literature regarding its use in tendon disorders. The biological potential of these materials can be harnessed and administered into injured tissues, particularly in areas where standard healing is disrupted, a typical feature of Achilles tendinopathy. These products contain a wide variety of cell populations, cytokines, and growth factors, which have been shown to modulate many other cells at local and distal sites in the body. Collectively, they can shift the state of escalated inflammation and degeneration to reestablish tissue homeostasis. The typical features of Achilles tendinopathy are failed healing responses, persistent inflammation, and predominant catabolic reactions. Therefore, the application of orthobiologic tools represents a viable solution, considering their demonstrated efficacy, safety, and relatively easy manipulation. Perhaps a synergistic approach regarding the combination of these orthobiologics may promote more significant clinical outcomes rather than individual application. Although numerous optimistic results have been registered in the literature, additional studies and clinical trials are still highly desired to further illuminate the clinical utility and efficacy of these therapeutic strategies in the management of tendinopathies.

Keywords: Achilles tendinopathy; orthobiologics; regenerative medicine

ARTIGO

Stromal Vascular Fraction for Knee Osteoarthritis – An Update

- José Fábio Santos Duarte Lana
- Anna Vitória Santos Duarte Lana
- Lucas Furtado da Fonseca
- Marcelo Amaral Coelho
- Guilherme Gabriel Marques
- Tomas Mosaner
- Lucas Leite Ribeiro
- Gabriel Ohana Marques Azzini
- Gabriel Silva Santos
- Eduardo Fonseca
- Marco Antonio Percope de Andrade

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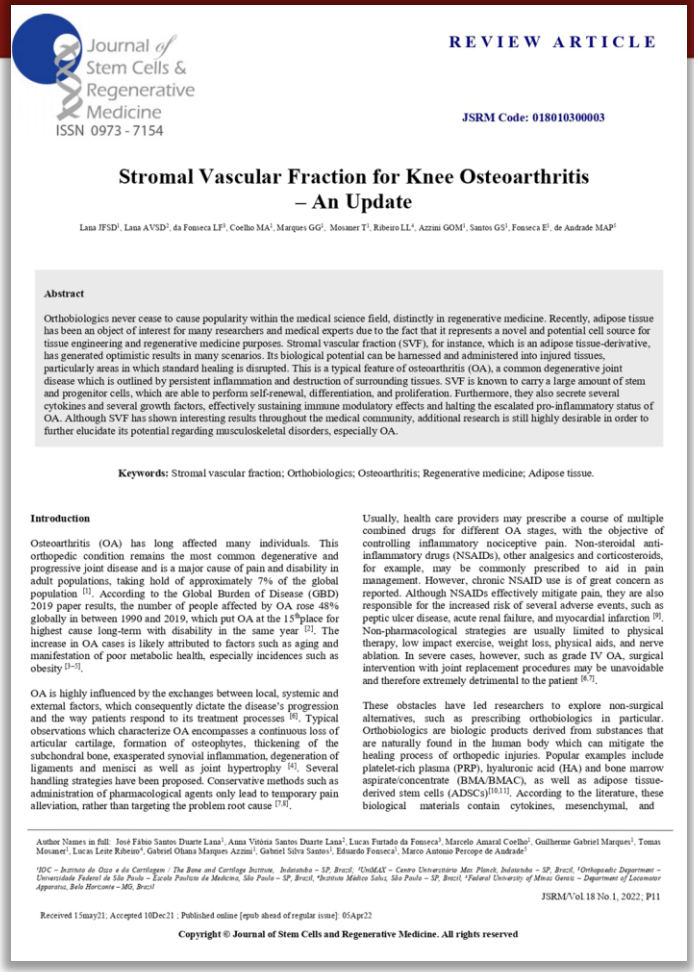

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REVIEW ARTICLE

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Stromal Vascular Fraction for Knee Osteoarthritis – An Update

Lana JFSD[1], Lana AVSD[2], da Fonseca LF[3], Coelho MA[2], Marques GG[2], Mosaner T[3], Ribeiro LL[4], Azzini GOM[3], Santos GS[3], Fonseca E[5], de Andrade MAP[1]

Abstract

Orthobiologics never cease to cause popularity within the medical science field, distinctly in regenerative medicine. Recently, adipose tissue has been an object of interest for many researchers and medical experts due to the fact that it represents a novel and potential cell source for tissue engineering and regenerative medicine purposes. Stromal vascular fraction (SVF), for instance, which is an adipose tissue-derivative, has generated optimistic results in many scenarios. Its biological potential can be harnessed and administered into injured tissues, particularly areas in which standard healing is disrupted. This is a typical feature of osteoarthritis (OA), a common degenerative joint disease which is outlined by persistent inflammation and destruction of surrounding tissues. SVF is known to carry a large amount of stem and progenitor cells, which are able to perform self-renewal, differentiation, and proliferation. Furthermore, they also secrete several cytokines and several growth factors, effectively sustaining immune modulatory effects and halting the escalated pro-inflammatory status of OA. Although SVF has shown interesting results throughout the medical community, additional research is still highly desirable in order to further elucidate its potential regarding musculoskeletal disorders, especially OA.

Keywords: Stromal vascular fraction; Orthobiologics; Osteoarthritis; Regenerative medicine; Adipose tissue.

Introduction

Osteoarthritis (OA) has long affected many individuals. This orthopedic condition remains the most common degenerative and progressive joint disease and is a major cause of pain and disability in adult populations, taking hold of approximately 7% of the global population [1]. According to the Global Burden of Disease (GBD) 2019 paper results, the number of people affected by OA rose 48% globally in between 1990 and 2019, which put OA at the 15th place for highest cause long-term with disability in the same year [2]. The increase in OA cases is likely attributed to factors such as aging and manifestation of poor metabolic health, especially incidences such as obesity [3–5].

OA is highly influenced by the exchanges between local, systemic and external factors, which consequently dictate the disease's progression and the way patients respond to its treatment processes [6]. Typical observations which characterize OA encompasses a continuous loss of articular cartilage, formation of osteophytes, thickening of the subchondral bone, exasperated synovial inflammation, degeneration of ligaments and menisci as well as joint hypertrophy [6]. Several handling strategies have been proposed. Conservative methods such as administration of pharmacological agents only lead to temporary pain alleviation, rather than targeting the problem root cause [7,8].

Usually, health care providers may prescribe a course of multiple combined drugs for different OA stages, with the objective of controlling inflammatory nociceptive pain. Non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics and corticosteroids, for example, may be commonly prescribed to aid in pain management. However, chronic NSAID use is of great concern as reported. Although NSAIDs effectively mitigate pain, they are also responsible for the increased risk of several adverse events, such as peptic ulcer disease, acute renal failure, and myocardial infarction [9]. Non-pharmacological strategies are usually limited to physical therapy, low impact exercise, weight loss, physical aids, and nerve ablation. In severe cases, however, such as grade IV OA, surgical intervention with joint replacement procedures may be unavoidable and therefore extremely detrimental to the patient [6,7].

These obstacles have led researchers to explore non-surgical alternatives, such as prescribing orthobiologics in particular. Orthobiologics are biologic products derived from substances that are naturally found in the human body which can mitigate the healing process of orthopedic injuries. Popular examples include platelet-rich plasma (PRP), hyaluronic acid (HA) and bone marrow aspirate/concentrate (BMA/BMAC), as well as adipose tissue-derived stem cells (ADSCs)[10,11]. According to the literature, these biological materials contain cytokines, mesenchymal, and

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ARTIGO

Application of Sygen® in Diabetic Peripheral Neuropathies—A Review of Biological Interactions

- Marcelo Amaral Coelho
- Madhan Jeyaraman
- Naveen Jeyaraman
- Ramya Lakshmi Rajendran
- André Atsushi Sugano
- Tomas Mosaner
- Gabriel Silva Santos
- João Vitor Bizinotto Lana
- Anna Vitória Santos Duarte Lana
- Lucas Furtado da Fonseca
- Rafael Barnabé Domingues
- Prakash Gangadaran
- Byeong-Cheol Ahn
- **José Fábio Santos Duarte Lana**

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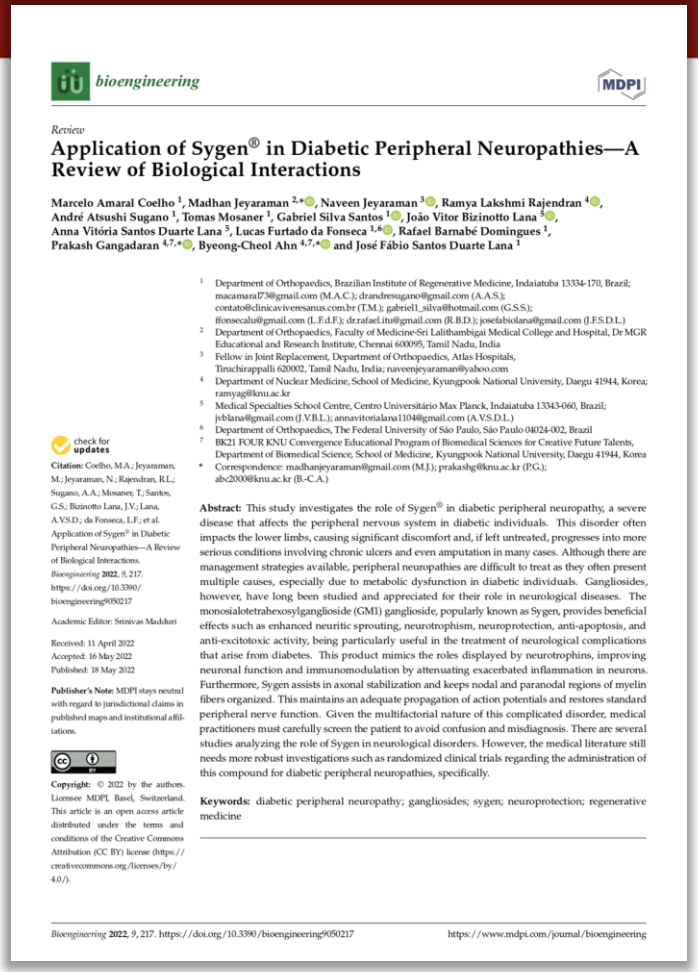

bioengineering

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Review

Application of Sygen® in Diabetic Peripheral Neuropathies—A Review of Biological Interactions

Marcelo Amaral Coelho [1], Madhan Jeyaraman [2,*], Naveen Jeyaraman [3], Ramya Lakshmi Rajendran [4], André Atsushi Sugano [1], Tomas Mosaner [1], Gabriel Silva Santos [1], João Vitor Bizinotto Lana [5], Anna Vitória Santos Duarte Lana [5], Lucas Furtado da Fonseca [1,6], Rafael Barnabé Domingues [1], Prakash Gangadaran [4,7,*], Byeong-Cheol Ahn [4,7,*] and José Fábio Santos Duarte Lana [1]

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Abstract: This study investigates the role of Sygen® in diabetic peripheral neuropathy, a severe disease that affects the peripheral nervous system in diabetic individuals. This disorder often impacts the lower limbs, causing significant discomfort and, if left untreated, progresses into more serious conditions involving chronic ulcers and even amputation in many cases. Although there are management strategies available, peripheral neuropathies are difficult to treat as they often present multiple causes, especially due to metabolic dysfunction in diabetic individuals. Gangliosides, however, have long been studied and appreciated for their role in neurological diseases. The monosialotetrahexosylganglioside (GM1) ganglioside, popularly known as Sygen, provides beneficial effects such as enhanced neuritic sprouting, neurotrophism, neuroprotection, anti-apoptosis, and anti-excitotoxic activity, being particularly useful in the treatment of neurological complications that arise from diabetes. This product mimics the roles displayed by neurotrophins, improving neuronal function and immunomodulation by attenuating exacerbated inflammation in neurons. Furthermore, Sygen assists in axonal stabilization and keeps nodal and paranodal regions of myelin fibers organized. This maintains an adequate propagation of action potentials and restores standard peripheral nerve function. Given the multifactorial nature of this complicated disorder, medical practitioners must carefully screen the patient to avoid confusion and misdiagnosis. There are several studies analyzing the role of Sygen in neurological disorders. However, the medical literature still needs more robust investigations such as randomized clinical trials regarding the administration of this compound for diabetic peripheral neuropathies, specifically.

Keywords: diabetic peripheral neuropathy; gangliosides; sygen; neuroprotection; regenerative medicine

ARTIGO

Platelet-rich plasma application in diabetic ulcers: A review

- Victoria Pereira Simão
- Carolina Souza Cury
- Gabriel Mota Zamariolli Tavares
- Gabriel Calixto Ortega
- Arthur Cichetto Ribeiro
- Gabriel Silva Santos
- **José Fábio Santos Duarte Lana**

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MINIREVIEWS

Platelet-rich plasma application in diabetic ulcers: A review

Victoria Pereira Simão, Carolina Souza Cury, Gabriel Mota Zamariolli Tavares, Gabriel Calixto Ortega, Arthur Cichetto Ribeiro, Gabriel Silva Santos, José Fábio Santos Duarte Lana

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Abstract

There are 422 million diabetic people in the world. 25% of these individuals are diagnosed with diabetic foot ulcer (DFU). 20% of patients with DFU will suffer amputation of the lower limbs. Following amputation procedures, the mortality rate of patients is over 70% in 5 years. Diabetes has no cure and, therefore, treatment aims to prevent and treat its complications. Autologous platelet-rich plasma (PRP) has been shown to be a therapeutic tool for many types of disorders, including the treatment of DFU. This manuscript aims to carry out a review to provide more knowledge about the efficacy and safety of autologous PRP for wound closure in patients with DFU. The majority of studies included in this review state that PRP promotes improvement of DFU lesions by accelerating tissue healing processes. However, many studies have a small sample size and thus require larger sample range in order to improve robustness of data in the literature.

Key Words: Diabetic foot ulcer; Platelet-rich plasma; Wound healing; Tissue regeneration; Inflammation

ARTIGO

Photobiomodulation therapy for osteoarthritis: Mechanisms of action

- Fábio Pericinoto Giolo
- Gabriel Silva Santos
- Victor Fontes Pacheco
- Stephany Cares Huber
- Kaue Franco Malange
- Bruno Lima Rodrigues
- Fernanda Bassora
- Tomas Mosaner
- Gabriel Azzini
- Lucas Leite Ribeiro
- Carlos Amilcar Parada
- **José Fábio Santos Duarte Lana**

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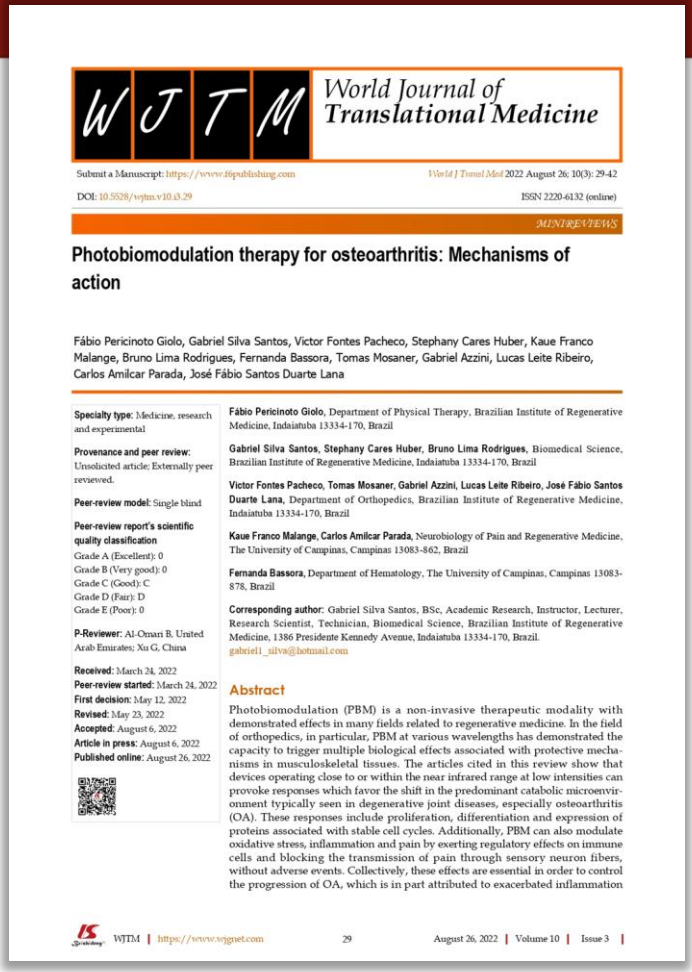

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MINIREVIEWS

Photobiomodulation therapy for osteoarthritis: Mechanisms of action

Fábio Pericinoto Giolo, Gabriel Silva Santos, Victor Fontes Pacheco, Stephany Cares Huber, Kaue Franco Malange, Bruno Lima Rodrigues, Fernanda Bassora, Tomas Mosaner, Gabriel Azzini, Lucas Leite Ribeiro, Carlos Amilcar Parada, José Fábio Santos Duarte Lana

Specialty type: Medicine, research and experimental

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Abstract

Photobiomodulation (PBM) is a non-invasive therapeutic modality with demonstrated effects in many fields related to regenerative medicine. In the field of orthopedics, in particular, PBM at various wavelengths has demonstrated the capacity to trigger multiple biological effects associated with protective mechanisms in musculoskeletal tissues. The articles cited in this review show that devices operating close to or within the near infrared range at low intensities can provoke responses which favor the shift in the predominant catabolic microenvironment typically seen in degenerative joint diseases, especially osteoarthritis (OA). These responses include proliferation, differentiation and expression of proteins associated with stable cell cycles. Additionally, PBM can also modulate oxidative stress, inflammation and pain by exerting regulatory effects on immune cells and blocking the transmission of pain through sensory neuron fibers, without adverse events. Collectively, these effects are essential in order to control the progression of OA, which is in part attributed to exacerbated inflammation

ARTIGO

The Mechanism of Action between Pulsed Radiofrequency and Orthobiologics: Is There a Synergistic Effect?

- Daniel de Moraes Ferreira Jorge
- Stephany Cares Huber
- Bruno Lima Rodrigues
- Lucas Furtado Da Fonseca
- Gabriel Ohana Marques Azzini
- Carlos Amilcar Parada
- Christian Paulus-Romero
- **José Fábio Santos Duarte Lana**

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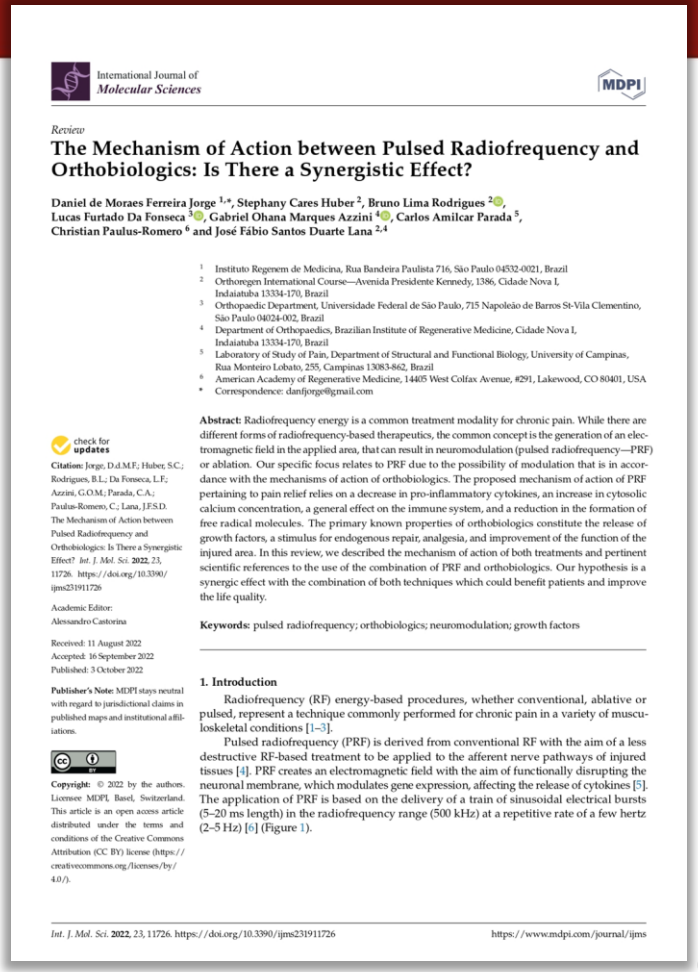

International Journal of Molecular Sciences
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Review

The Mechanism of Action between Pulsed Radiofrequency and Orthobiologics: Is There a Synergistic Effect?

Daniel de Moraes Ferreira Jorge [1,*], Stephany Cares Huber [2], Bruno Lima Rodrigues [2], Lucas Furtado Da Fonseca [3], Gabriel Ohana Marques Azzini [4], Carlos Amilcar Parada [5], Christian Paulus-Romero [6] and José Fábio Santos Duarte Lana [2,4]

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Abstract: Radiofrequency energy is a common treatment modality for chronic pain. While there are different forms of radiofrequency-based therapeutics, the common concept is the generation of an electromagnetic field in the applied area, that can result in neuromodulation (pulsed radiofrequency—PRF) or ablation. Our specific focus relates to PRF due to the possibility of modulation that is in accordance with the mechanisms of action of orthobiologics. The proposed mechanism of action of PRF pertaining to pain relief relies on a decrease in pro-inflammatory cytokines, an increase in cytosolic calcium concentration, a general effect on the immune system, and a reduction in the formation of free radical molecules. The primary known properties of orthobiologics constitute the release of growth factors, a stimulus for endogenous repair, analgesia, and improvement of the function of the injured area. In this review, we described the mechanism of action of both treatments and pertinent scientific references to the use of the combination of PRF and orthobiologics. Our hypothesis is a synergic effect with the combination of both techniques which could benefit patients and improve the life quality.

Keywords: pulsed radiofrequency; orthobiologics; neuromodulation; growth factors

1. Introduction

Radiofrequency (RF) energy-based procedures, whether conventional, ablative or pulsed, represent a technique commonly performed for chronic pain in a variety of musculoskeletal conditions [1–3].

Pulsed radiofrequency (PRF) is derived from conventional RF with the aim of a less destructive RF-based treatment to be applied to the afferent nerve pathways of injured tissues [4]. PRF creates an electromagnetic field with the aim of functionally disrupting the neuronal membrane, which modulates gene expression, affecting the release of cytokines [5]. The application of PRF is based on the delivery of a train of sinusoidal electrical bursts (5–20 ms length) in the radiofrequency range (500 kHz) at a repetitive rate of a few hertz (2–5 Hz) [6] (Figure 1).

ARTIGO

Full Recovery from O'Donoghue's Triad with Autologous Bone Marrow Aspirate Matrix: A Case Report

- **José Fábio Santos Duarte Lana**
- André Atsushi Sugano
- Henrique Valadão De Barros
- Tomas Mosaner
- Gabriel Silva Santos
- João Vitor Bizinotto Lana
- Rodrigo Vicente
- Marco Antônio Percope De Andrade

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Pesquisa completa aqui!

Journal of Functional Morphology and Kinesiology
MDPI

Case Report

Full Recovery from O'Donoghue's Triad with Autologous Bone Marrow Aspirate Matrix: A Case Report

José Fábio Santos Duarte Lana [1], André Atsushi Sugano [1], Henrique Valadão De Barros [2], Tomas Mosaner [1], Gabriel Silva Santos [1,*], João Vitor Bizinotto Lana [1], Rodrigo Vicente [1] and Marco Antônio Percope De Andrade [3]

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Abstract: O'Donoghue's triad is an extremely debilitating condition. Although there are many conventional treatments available, there is still no consensus regarding the most effective rehabilitation protocol for a full recovery. Surgical interventions have become an ordinary consideration, but problems may still persist even after the surgical procedure. Orthobiologics, however, have gained considerable popularity in regenerative medicine. Notable autologous alternatives, such as bone marrow aspirate (BMA), are often utilized in clinical settings. To our knowledge, the administration of BMA products for the management of O'Donoghue's triad has not been thoroughly investigated in the literature. In this case report we describe a full recovery from O'Donoghue's triad with BMA matrix in a patient who was recalcitrant to surgical intervention due to fear of complications. Our patient received three BMA matrix injections with four-week intervals, exhibiting significant recovery according to pain scores, functional assessment outcomes, and magnetic resonance imaging (MRI) results. The patient returned to normal activities with no complaints and MRI evidence at follow-up showed significant signs of structural restoration of the musculoskeletal tissues. Here, we demonstrate that autologous BMA products are a feasible alternative for the accelerated recovery of musculoskeletal tissue injury with safety and efficacy.

Keywords: case report; knee injury; anterior cruciate ligament; orthobiologics; bone marrow aspirate

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1. Introduction

ACL ruptures can occur in contact sports and also in noncontact situations during sudden direction changes, cutting maneuvers, or during landing after a jump. Few prospective studies have investigated the biomechanical risk factors of ACL injuries, but it seems that the injury is linked to poor neuromuscular control of the knee-stabilizing muscles and to the dynamic valgus condition to which the knee can be subjected even in the context of contact sports [1]. This severe injury usually affects proximal structures, including the menisci, surrounding musculature, critical neurovascular structures, and other ligaments [2]. Moreover, it is also related to a higher risk of a knee re-injury and long-term medical disability due to early osteoarthritis occurring in half of the individuals 10–15 years later [3]. The ACL is a pivotal structure in knee joints and its main function is to avoid anterior translation of the tibia. It also stabilizes internal tibial rotation and valgus angulation at the knee [2]. Upon complete extension, the ACL can absorb up to 75% of loading and approximately 85% between 30 and 90 degrees of flexion [2]. ACL injuries promote biomechanical instability and reduced magnitude of coupled rotation during flexion. For reference, the tensile strength of this ligament is of about 2200 Newtons; however, this threshold may change due to advanced age and repetitive loading. ACL force increases in equal proportion to the increasing magnitude of the anterior drawer force [4].

ARTIGO

Extracorporeal Shockwave Treatment for Low Back Pain: A Descriptive Review of The Literature

- Claudio Lopes Simplicio
- Gabriel Santos
- Gilson Tanaka Shinzato
- Guilherme Antonio Moreira de Barros
- Marta Imamura
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- **José Fábio Santos Duarte Lana**

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Veículo: Biologic Orthopedic Journal

Pesquisa completa aqui!

Biologic Orthopedic Journal

Review Article
DOI: 10.22374/boj.v4iSP1.46

EXTRACORPOREAL SHOCKWAVE TREATMENT FOR LOW BACK PAIN: A DESCRIPTIVE REVIEW OF THE LITERATURE

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Abstract

Low back pain is a common symptom in patients with chronic musculoskeletal conditions, affecting several individuals. In most cases, low back pain can often prove to be nonspecific or even multifactorial. Current treatment approach is based on surgical and noninvasive interventions, including pharmacological, psychological, physiotherapeutic, or complementary strategies. Extracorporeal shock wave therapy (ESWT) is a type of noninvasive mechanotherapy that has become popular in recent years due to its applicability in the treatment of various musculoskeletal disorders, especially in the lumbar spine of individuals with osteoporosis, sacroiliitis, and even spinal cord disorders. The objective of this manuscript is to review the scientific evidence supporting the application of this therapy in the management of low back pain, and give a brief description of the treatment techniques used in clinical settings. The articles included in this descriptive review were selected from databases using the Google Scholar tool, from which a total of 13 applicable studies matching the topic were included. Despite the need for more clinical trials, shock waves have been applied in medical health for many years with satisfactory results. Its application in the treatment of lumbar spine disorders has been shown to be advantageous in the management of pathological progression, such as the natural wear and tear process of musculoskeletal structures. In this sense, shockwave therapy may represent a viable alternative for the treatment of lumbar spine disorders; however, its therapeutic effects and mechanisms require further elucidation.

Keywords: *low back pain; shockwave therapy; regenerative medicine; orthopedics; musculoskeletal medicine*

Bio Ortho J Vol 4(SP1):e96–e105; 5 December, 2022.

ARTIGO

Platelet-Rich Plasma Gel Matrix (PRP-GM): Description of a New Technique

- Thales Thiago Ferreira Godoi
- Bruno Lima Rodrigues
- Stephany Cares Huber
- Maria Helena Andrade Santana
- Lucas Furtado da Fonseca
- Gabriel Silva Santos
- Gabriel Ohana Marques Azzini
- Tomas Mosaner
- Chris Paulus-Romero
- **José Fábio Santos Duarte Lana**

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Veículo: MDPI - Bioengineering

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bioengineering

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Technical Note

Platelet-Rich Plasma Gel Matrix (PRP-GM): Description of a New Technique

Thales Thiago Ferreira Godoi [1], Bruno Lima Rodrigues [2], Stephany Cares Huber [2], Maria Helena Andrade Santana [3], Lucas Furtado da Fonseca [1,2], Gabriel Silva Santos [2,*], Gabriel Ohana Marques Azzini [2], Tomas Mosaner [4], Chris Paulus-Romero [5] and José Fábio Santos Duarte Lana [2]

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Abstract: Several musculoskeletal conditions are triggered by inflammatory processes that occur along with imbalances between anabolic and catabolic events. Platelet-rich plasma (PRP) is an autologous product derived from peripheral blood with inherent immunomodulatory and anabolic properties. The clinical efficacy of PRP has been evaluated in several musculoskeletal conditions, including osteoarthritis, tendinopathy, and osteonecrosis. When used in combination with hyaluronic acid (HA), a common treatment alternative, the regenerative properties of PRP are significantly enhanced and may provide additional benefits in terms of clinical outcomes. Recently, a new PRP-derived product has been reported in the literature and is being referred to as "plasma gel". Plasma gels are obtained by polymerizing plasmatic proteins, which form solid thermal aggregates cross-linked with fibrin networks. Plasma gels are considered to be a rich source of growth factors and provide chemotactic, migratory, and proliferative properties. Additionally, clot formation and the associated fibrinolytic reactions play an additional role in tissue repair. There are only a few scientific articles focusing on plasma gels. Historically, they have been utilized in the fields of aesthetics and dentistry. Given that the combination of three products (PRP, HA, and plasma gel) could enhance tissue repair and wound healing, in this technical note, we propose a novel regenerative approach, named "PRP–HA cellular gel matrix" (PRP-GM), in which leukocyte-rich PRP (LR-PRP) is mixed with a plasma gel (obtained by heating the plasma up) and HA in one syringe using a three-way stopcock. The final product contains a fibrin–albumin network entangled with HA's polymers, in which the cells and biomolecules derived from PRP are attached and released gradually as fibrinolytic reactions and hyaluronic acid degradation occur. The presence of leukocytes, especially monocytes and macrophages, promotes tissue regeneration, as type 2 macrophages (M2) possess an anti-inflammatory feature. In addition, HA promotes the viscosupplementation of the joint and induces an anti-inflammatory response, resulting in pain relief. This unique combination of biological molecules may contribute to the optimization of regenerative protocols suitable for the treatment of degenerative musculoskeletal diseases.

Keywords: platelet-rich plasma; hyaluronic acid; autologous biomaterials; regenerative medicine; orthopedics

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Citation: Godoi, T.T.F.; Rodrigues, B.L.; Huber, S.C.; Santana, M.H.A.; da Fonseca, L.F.; Santos, G.S.; Azzini, G.O.M.; Mosaner, T.; Paulus-Romero, C.; Lana, J.F.S.D. Platelet-Rich Plasma Gel Matrix (PRP-GM): Description of a New Technique. *Bioengineering* **2022**, *9*, 817. https://doi.org/10.3390/bioengineering9120817

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1. Introduction

Platelet-rich plasma (PRP) is an autologous product derived from peripheral blood, in which the platelet number is concentrated above the whole blood levels [1]. In the field of regenerative medicine, the biological function of platelets extends beyond hemostasis; their dense granules contain ADP, ATP, serotonin, and calcium, whereas their alpha granules are rich in chemotactic factors, growth factors, and immunomodulatory cytokines [2].

ARTIGO

Bone Marrow Aspirate Concentrate Improves Outcomes in Adults With Osteochondral Dissecans of the Talus and Achilles Rupture

- Raffael Marum Bachir
- Isabella Martins Zaia
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- Guilherme Boni, M.
- Rodrigo Fernando Guercia
- Gabriel Ferraz Ferreira
- **José Fábio Santos Duarte Lana**

Publicação: Março de 2023
Veículo: The Journal of Artroscopy and Related Surgery

Pesquisa completa aqui!

Systematic Review

Bone Marrow Aspirate Concentrate Improves Outcomes in Adults With Osteochondral Dissecans of the Talus and Achilles Rupture

Raffael Marum Bachir, M.D., Isabella Martins Zaia, M.D., Gabriel Silva Santos, B.Sc., Lucas Furtado da Fonseca, M.D., Guilherme Boni, M.D., Rodrigo Fernando Guercia, M.D., Gabriel Ferraz Ferreira, M.D., and José Fabio Santos Duarte Lana, M.D.

Purpose: The objective of this systematic literature review was to investigate the effects of the clinical application of bone marrow aspirate (BMA) and/or bone marrow aspirate concentrate (BMAC) in tendon and cartilage injuries in the foot and ankle. **Methods:** A search of the Embase, MEDLINE/PubMed, CINAHL, and Cochrane databases was performed in January 2021. The risk of bias of the studies was assessed using the tool "A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies." The outcomes analyzed included pain reduction and functional improvement with the use of BMA/BMAC in patients with tendon and cartilage injuries in the foot and ankle. **Results:** Eleven studies met the inclusion criteria for analysis, involving a total of 527 subjects with osteochondral lesions (OCLs) of the talus, cartilage lesions of the talus, and acute Achilles tendon rupture. BMAC was applied alone in 4 studies, and in 7 studies, it was compared with other techniques such as matrix-induced autologous chondrocyte implantation, particulate juvenile articular cartilage, or microfracture. Interventions demonstrated improved function and reduced foot and ankle pain and showed no serious adverse effects. **Conclusions:** Evidence indicates that BMAC provides good clinical results, with improved function and reduced pain in adults with OCL and cartilage lesions of the talus and acute Achilles tendon rupture. **Level of Evidence:** Level IV, systematic review of level II to IV studies.

The feet and ankles can be affected by acute and chronic traumatic injuries to bones, ligaments, and tendons, as well as degenerative changes and inflammatory conditions that result in pain and functional disability.[1-3] In this sense, foot and ankle surgeons diagnose and treat different diseases conservatively or surgically.[4] Treatment options include surgical procedures with reparative or restorative techniques and pharmacologic and nonpharmacologic treatments that can be used to reduce pain, maintain function, accommodate existing deformity, and prevent new deformities.[1,5,6] In addition, recent research has demonstrated that biological agents can provide excellent clinical results by optimizing and accelerating the healing of musculoskeletal tissue.[7] Available biological treatments include bone marrow aspirate/bone marrow aspirate concentrate (BMA/BMAC), mesenchymal stem/stromal cells (MSCs), autologous blood products such as platelet-rich plasma, autologous chondrocyte implantation, and autologous matrix-induced chondrogenesis.[4,7] Most of these treatments have shown promising results in relation to bone and cartilage regeneration.[8]

BMA and BMAC emerged as feasible alternatives to orthoplastic reconstruction. MSCs, growth factors, and other bone marrow–derived biological components can be found in bone marrow products. Notable effects include enhanced proliferation and angiogenesis as well as impeded secretion of proinflammatory cytokines.[9,10] Thus, considering both the anti-inflammatory and regenerative effect, BMA and BMAC can be an important treatment for cartilage regeneration.

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ARTIGO

Intra-Articular Hyaluronic Acid in Osteoarthritis and Tendinopathies: Molecular and Clinical Approaches

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- Mariana Ramos Costa Marques
- Vinicius Calumby Costa
- Gabriel Silva Santos
- Rubens Andrade Martins
- Marcia da Silva Santos
- Maria Helena Andrade Santana
- Arulkumar Nallakumarasamy
- Madhan Jeyaraman
- João Vitor Bizinotto Lana
- **José Fábio Santos Duarte Lana**

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Veículo: MDPI - Biomedicines

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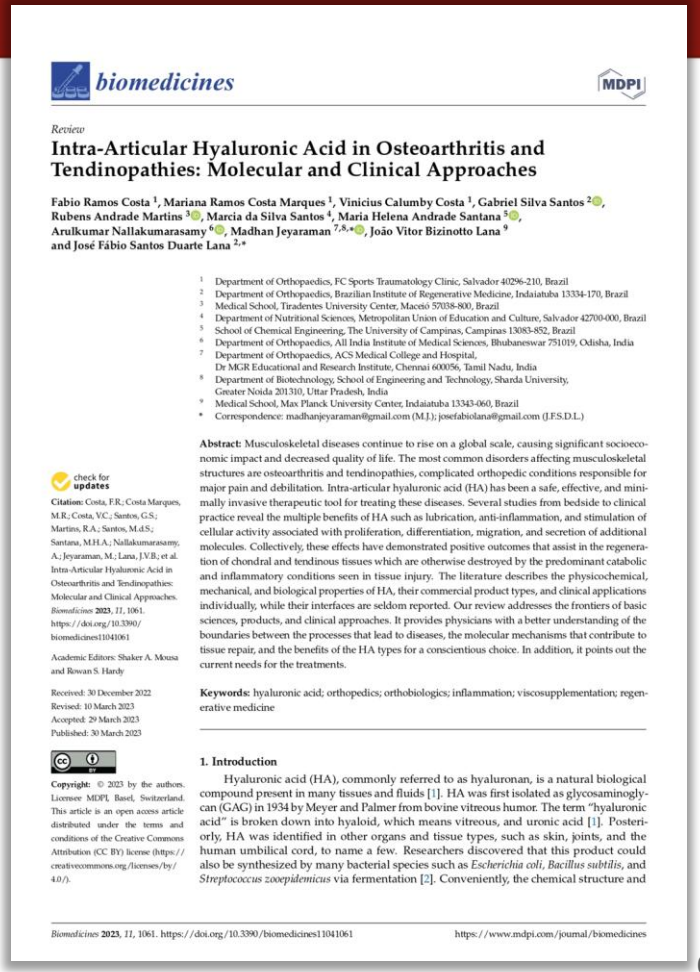

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Review

Intra-Articular Hyaluronic Acid in Osteoarthritis and Tendinopathies: Molecular and Clinical Approaches

Fabio Ramos Costa [1], Mariana Ramos Costa Marques [1], Vinicius Calumby Costa [1], Gabriel Silva Santos [2], Rubens Andrade Martins [3], Marcia da Silva Santos [4], Maria Helena Andrade Santana [5], Arulkumar Nallakumarasamy [6], Madhan Jeyaraman [7,8,*], João Vitor Bizinotto Lana [9] and José Fábio Santos Duarte Lana [2,*]

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Abstract: Musculoskeletal diseases continue to rise on a global scale, causing significant socioeconomic impact and decreased quality of life. The most common disorders affecting musculoskeletal structures are osteoarthritis and tendinopathies, complicated orthopedic conditions responsible for major pain and debilitation. Intra-articular hyaluronic acid (HA) has been a safe, effective, and minimally invasive therapeutic tool for treating these diseases. Several studies from bedside to clinical practice reveal the multiple benefits of HA such as lubrication, anti-inflammation, and stimulation of cellular activity associated with proliferation, differentiation, migration, and secretion of additional molecules. Collectively, these effects have demonstrated positive outcomes that assist in the regeneration of chondral and tendinous tissues which are otherwise destroyed by the predominant catabolic and inflammatory conditions seen in tissue injury. The literature describes the physicochemical, mechanical, and biological properties of HA, their commercial product types, and clinical applications individually, while their interfaces are seldom reported. Our review addresses the frontiers of basic sciences, products, and clinical approaches. It provides physicians with a better understanding of the boundaries between the processes that lead to diseases, the molecular mechanisms that contribute to tissue repair, and the benefits of the HA types for a conscientious choice. In addition, it points out the current needs for the treatments.

Keywords: hyaluronic acid; orthopedics; orthobiologics; inflammation; viscosupplementation; regenerative medicine

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1. Introduction

Hyaluronic acid (HA), commonly referred to as hyaluronan, is a natural biological compound present in many tissues and fluids [1]. HA was first isolated as glycosaminoglycan (GAG) in 1934 by Meyer and Palmer from bovine vitreous humor. The term "hyaluronic acid" is broken down into hyaloid, which means vitreous, and uronic acid [1]. Posteriorly, HA was identified in other organs and tissue types, such as skin, joints, and the human umbilical cord, to name a few. Researchers discovered that this product could also be synthesized by many bacterial species such as *Escherichia coli*, *Bacillus subtilis*, and *Streptococcus zooepidemicus* via fermentation [2]. Conveniently, the chemical structure and

ARTIGO

Cannabidiol for musculoskeletal regenerative medicine

- Gabriel Ohana Marques Azzini
- Vitor Ohana Marques Azzini
- Gabriel Silva Santos
- Silvia Visoni
- Maria Alice Fusco
- Natascha Szumsztajn Beker
- Ansar Mahmood
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- Madhan Jeyaraman
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- Naveen Jeyaraman
- Lucas Furtado da Fonseca
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- Rodrigo Vicente
- Ramya Lakshmi Rajendran
- Prakash Gangadaran
- Byeong-Cheol Ahn
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Publicação: 09 de Maio de 2023
Veículo: Experimental Biology and Medicine

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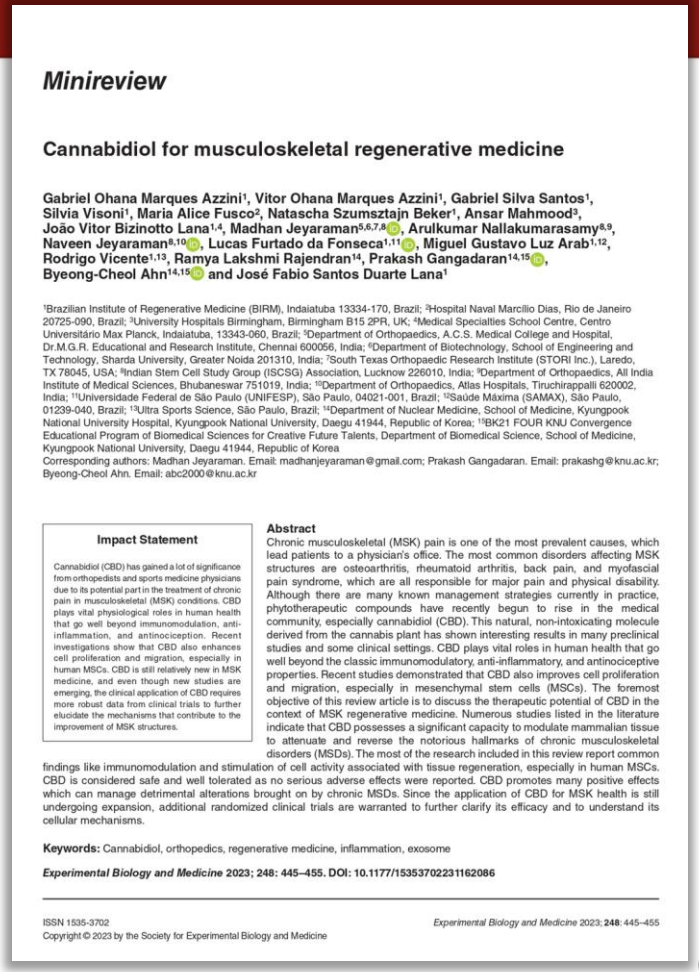

Minireview

Cannabidiol for musculoskeletal regenerative medicine

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Impact Statement

Cannabidiol (CBD) has gained a lot of significance from orthopedists and sports medicine physicians due to its potential part in the treatment of chronic pain in musculoskeletal (MSK) conditions. CBD plays vital physiological roles in human health that go well beyond immunomodulation, anti-inflammation, and antinociception. Recent investigations show that CBD also enhances cell proliferation and migration, especially in human MSCs. CBD is still relatively new in MSK medicine, and even though new studies are emerging, the clinical application of CBD requires more robust data from clinical trials to further elucidate the mechanisms that contribute to the improvement of MSK structures.

Abstract

Chronic musculoskeletal (MSK) pain is one of the most prevalent causes, which lead patients to a physician's office. The most common disorders affecting MSK structures are osteoarthritis, rheumatoid arthritis, back pain, and myofascial pain syndrome, which are all responsible for major pain and physical disability. Although there are many known management strategies currently in practice, phytotherapeutic compounds have recently begun to rise in the medical community, especially cannabidiol (CBD). This natural, non-intoxicating molecule derived from the cannabis plant has shown interesting results in many preclinical studies and some clinical settings. CBD plays vital roles in human health that go well beyond the classic immunomodulatory, anti-inflammatory, and antinociceptive properties. Recent studies demonstrated that CBD also improves cell proliferation and migration, especially in mesenchymal stem cells (MSCs). The foremost objective of this review article is to discuss the therapeutic potential of CBD in the context of MSK regenerative medicine. Numerous studies listed in the literature indicate that CBD possesses a significant capacity to modulate mammalian tissue to attenuate and reverse the notorious hallmarks of chronic musculoskeletal disorders (MSDs). The most of the research included in this review report common findings like immunomodulation and stimulation of cell activity associated with tissue regeneration, especially in human MSCs. CBD is considered safe and well tolerated as no serious adverse effects were reported. CBD promotes many positive effects which can manage detrimental alterations brought on by chronic MSDs. Since the application of CBD for MSK health is still undergoing expansion, additional randomized clinical trials are warranted to further clarify its efficacy and to understand its cellular mechanisms.

Keywords: Cannabidiol, orthopedics, regenerative medicine, inflammation, exosome

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ARTIGO

Angiogenesis and Tissue Repair Depend on Platelet Dosing and Bioformulation Strategies Following Orthobiological Platelet-Rich Plasma Procedures: A Narrative Review

- Peter A. Everts
- **José Fábio Lana**
- Kentaro Onishi
- Don Buford
- Jeffrey Peng
- Ansar Mahmood
- Lucas F. Fonseca
- Andre van Zundert
- Luga Podesta

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Veículo: MDPI - Biomedicines

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Review

Angiogenesis and Tissue Repair Depend on Platelet Dosing and Bioformulation Strategies Following Orthobiological Platelet-Rich Plasma Procedures: A Narrative Review

Peter A. Everts [1,2,*], José Fábio Lana [2,3], Kentaro Onishi [4], Don Buford [5], Jeffrey Peng [6], Ansar Mahmood [7], Lucas F. Fonseca [8], Andre van Zundert [9] and Luga Podesta [10]

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Abstract: Angiogenesis is the formation of new blood vessel from existing vessels and is a critical first step in tissue repair following chronic disturbances in healing and degenerative tissues. Chronic pathoanatomic tissues are characterized by a high number of inflammatory cells; an overexpression of inflammatory mediators; such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1); the presence of mast cells, T cells, reactive oxygen species, and matrix metalloproteinases; and a decreased angiogenic capacity. Multiple studies have demonstrated that autologous orthobiological cellular preparations (e.g., platelet-rich plasma (PRP)) improve tissue repair and regenerate tissues. There are many PRP devices on the market. Unfortunately, they differ greatly in platelet numbers, cellular composition, and bioformulation. PRP is a platelet concentrate consisting of a high concentration of platelets, with or without certain leukocytes, platelet-derived growth factors (PGFs), cytokines, molecules, and signaling cells. Several PRP products have immunomodulatory capacities that can influence resident cells in a diseased microenvironment, inducing tissue repair or regeneration. Generally, PRP is a blood-derived product, regardless of its platelet number and bioformulation, and the literature indicates both positive and negative patient treatment outcomes. Strangely, the literature does not designate specific PRP preparation qualifications that can potentially contribute to tissue repair. Moreover, the literature scarcely addresses the impact of platelets and leukocytes in PRP on (neo)angiogenesis, other than a general one-size-fits-all statement that "PRP has angiogenic capabilities". Here, we review the cellular composition of all PRP constituents, including leukocytes, and describe the importance of platelet dosing and bioformulation strategies in orthobiological applications to initiate angiogenic pathways that re-establish microvasculature networks, facilitating the supply of oxygen and nutrients to impaired tissues.

Keywords: angiogenesis; tissue repair; platelet-rich plasma; platelet dose; bioformulation; leukocytes; platelet-rich fibrin; orthobiology; biosurgery

ARTIGO

Platelet-Rich Plasma Power-Mix Gel (ppm)—An Orthobiologic Optimization Protocol Rich in Growth Factors and Fibrin

- José Fábio Lana
- Joseph Purita
- Peter Albert Everts
- Palmerindo Antonio Tavares De Mendonça Neto
- Daniel de Moraes Ferreira Jorge
- Tomas Mosaner
- Stephany Cares Huber
- Gabriel Ohana Marques Azzini
- Lucas Furtado da Fonseca
- Madhan Jeyaraman
- Ignacio Dallo
- Gabriel Silva Santos

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Review

Platelet-Rich Plasma Power-Mix Gel (ppm)—An Orthobiologic Optimization Protocol Rich in Growth Factors and Fibrin

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Abstract: Platelet- and fibrin-rich orthobiologic products, such as autologous platelet concentrates, have been extensively studied and appreciated for their beneficial effects on multiple conditions. Platelet-rich plasma (PRP) and its derivatives, including platelet-rich fibrin (PRF), have demonstrated encouraging outcomes in clinical and laboratory settings, particularly in the treatment of musculoskeletal disorders such as osteoarthritis (OA). Although PRP and PRF have distinct characteristics, they share similar properties. The relative abundance of platelets, peripheral blood cells, and molecular components in these orthobiologic products stimulates numerous biological pathways. These include inflammatory modulation, augmented neovascularization, and the delivery of pro-anabolic stimuli that regulate cell recruitment, proliferation, and differentiation. Furthermore, the fibrinolytic system, which is sometimes overlooked, plays a crucial role in musculoskeletal regenerative medicine by regulating proteolytic activity and promoting the recruitment of inflammatory cells and mesenchymal stem cells (MSCs) in areas of tissue regeneration, such as bone, cartilage, and muscle. PRP acts as a potent signaling agent; however, it diffuses easily, while the fibrin from PRF offers a durable scaffolding effect that promotes cell activity. The combination of fibrin with hyaluronic acid (HA), another well-studied orthobiologic product, has been shown to improve its scaffolding properties, leading to more robust fibrin polymerization. This supports cell survival, attachment, migration, and proliferation. Therefore, the administration of the "power mix" containing HA and autologous PRP + PRF may prove to be a safe and cost-effective approach in regenerative medicine.

Keywords: platelet-rich plasma; platelet-rich fibrin; hyaluronic acid; orthobiologics; osteoarthritis; regenerative medicine

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1. Introduction

Osteoarthritis (OA) is acknowledged as a major degenerative and progressive joint disease responsible for significant pain and disability in the adult population [1]. The incidence of OA across the globe has risen significantly in the last few decades due to metabolic syndrome and aging [2–4]. This disease can often be challenging to treat as it presents a multifactorial nature, being mainly characterized by the physiological and architectural changes in the joint compartment as a whole [5]. It is highly influenced

ARTIGO

Recovery of Achilles Tendon Rupture with Bone Marrow Aspirate Matrix: A Case Report

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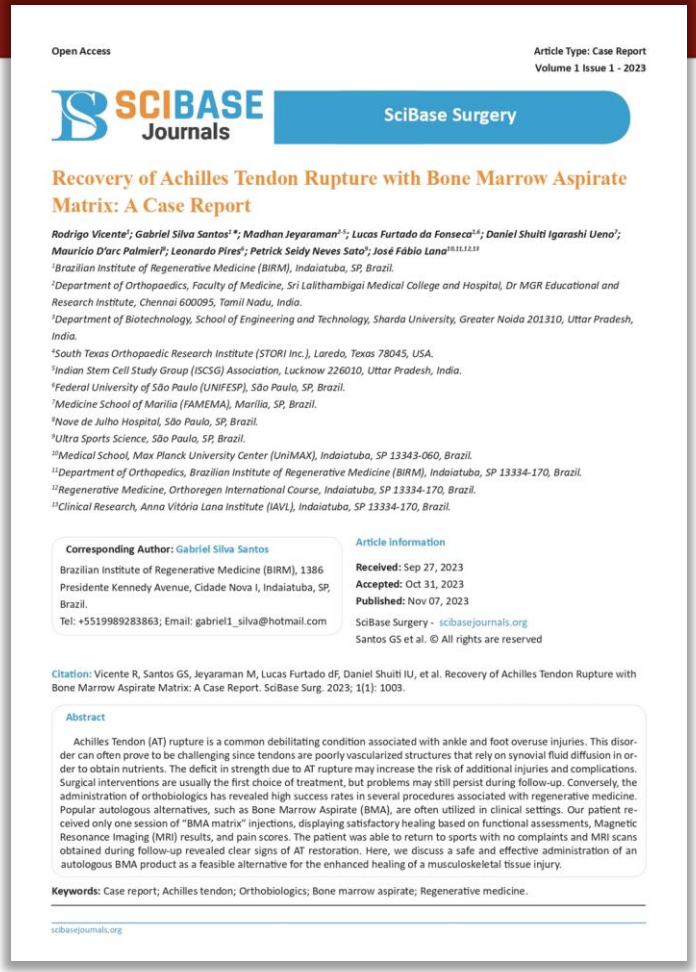

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SCIBASE Journals

SciBase Surgery

Recovery of Achilles Tendon Rupture with Bone Marrow Aspirate Matrix: A Case Report

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Abstract

Achilles Tendon (AT) rupture is a common debilitating condition associated with ankle and foot overuse injuries. This disorder can often prove to be challenging since tendons are poorly vascularized structures that rely on synovial fluid diffusion in order to obtain nutrients. The deficit in strength due to AT rupture may increase the risk of additional injuries and complications. Surgical interventions are usually the first choice of treatment, but problems may still persist during follow-up. Conversely, the administration of orthobiologics has revealed high success rates in several procedures associated with regenerative medicine. Popular autologous alternatives, such as Bone Marrow Aspirate (BMA), are often utilized in clinical settings. Our patient received only one session of "BMA matrix" injections, displaying satisfactory healing based on functional assessments, Magnetic Resonance Imaging (MRI) results, and pain scores. The patient was able to return to sports with no complaints and MRI scans obtained during follow-up revealed clear signs of AT restoration. Here, we discuss a safe and effective administration of an autologous BMA product as a feasible alternative for the enhanced healing of a musculoskeletal tissue injury.

Keywords: Case report; Achilles tendon; Orthobiologics; Bone marrow aspirate; Regenerative medicine.

ARTIGO

Bone Marrow Aspirate and Injectable Platelet Rich Fibrin for Achilles Tendon Rupture

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Pesquisa completa aqui!

Lana, et al. J Regen Med Med 2023, 12:6

Journal of Regenerative Medicine

Mini Review

A SCITECHNOL J OURNAL

Bone Marrow Aspirate and Injectable Platelet Rich Fibrin for Achilles Tendon Rupture

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Abstract

A chilles tendon rupture is a frequent ailment tied to overuse injuries of the ankle and foot. Given the tendon's limited vascularization, which depends on diffusion from synovial fluid for nutrient intake, managing this condition poses challenges. The weakened state post-rupture can predispose one to further injuries. Although surgical interventions often lead the way in treatment, challenges can arise during recovery. Meanwhile, the use of orthobiologics for non-invasive treatment has shown promising outcomes in various regenerative medicine applications. Notably, autologous treatments like bone marrow aspirate (BMA) and injectable platelet-rich fibrin (i-PRF) have gained traction in clinical scenarios.

BMA is a reservoir of diverse cell populations and molecules pivotal for tissue regeneration. PRF, on the other hand, is a dense concoction of platelets, growth factors, cytokines, leukocytes, and a sturdy fibrin matrix conducive to cellular functions.

Utilizing a combination of these two orthobiologic entities could amplify their individual effects, optimizing the healing process by fostering tissue growth, fostering new blood vessel formation, and modulating immune responses.

With this understanding, we advocate for the joint use of BMA and i-PRF as a potent orthobiologic solution, aiming to improve the healing trajectory of Achilles tendon ruptures within the sphere of regenerative orthopedics.

Keywords

Achilles tendon rupture; Bone marrow aspirate; Platelet-rich fibrin; Orthobiologics; Regenerative medicine.

Introduction

Achilles tendon rupture is a relatively common injury that occurs when the tendon, located at the back of the ankle, tears or ruptures. This injury can have a significant impact on mobility and athletic performance. Epidemiologically, Achilles tendon ruptures are most commonly seen in middle-aged individuals, particularly males, who participate in physical activities that involve repetitive jumping or sudden changes in direction. The prevalence of Achilles tendon ruptures is estimated to be around 18 to 37 cases per 100,000 people per year, with an increasing incidence noted in recent years [1-2] .

The Achilles tendon is the thickest and strongest tendon in the human body. It originates in the calf region, specifically from the fusion of the gastrocnemius muscle and the soleus muscle. The gastrocnemius muscle has two heads, medial and lateral, which cross the knee joint. Deep to the gastrocnemius lies the soleus muscle. Together, these muscles form the triceps surae, and their conjoint tendon is known as the Achilles tendon [1- 3] .The Achilles tendon has three main vascular areas: the peroneal artery supplies the midsection of the tendon, while the posterior tibial artery supplies the proximal and distal sections. The mid-substance of the tendon has relatively poor vascularization, which may contribute to a higher incidence of pathology in that region [1-3] .

The length of the Achilles tendon averages about 15 cm, with variations ranging from 11 to 26 cm. Its width changes along its course: it measures around 6.8 cm (4.5–8.6 cm) at its origin and narrows to approximately 1.8 cm (range 1.2–2.6 cm) in the midsection. As it approaches the calcaneus (heel bone), the Achilles tendon becomes more rounded and has a width of about 3.4 cm (2.0–4.8 cm) at its insertion site on the posterior surface of the calcaneus. [1-3] The Achilles tendon is connected to both the soleus and gastrocnemius muscles. The exact proportion of these insertions varies among individuals. Studies on cadavers have shown that in approximately 52% of cases, 52% of the tendon fibers originate from the soleus muscle, while 48% come from the gastrocnemius muscle. In 35% of cases, an equal contribution is observed, and in 13% of cadavers, more than 60% of the contribution arises from the gastrocnemius muscle [1-3].

The main motivation for the development of this study is based on the favorable results that researchers have obtained with the use of autologous products derived from bone marrow aspirate (BMA) and platelet concentrates such as platelet-rich fibrin (PRF) in accelerating the healing process and improving degenerative conditions. We believe that the association of the rich cellular and molecular components from BMA and PRF might establish an effective therapeutic methodology for the treatment of patients with Achilles tendon rupture.

Etiopathogenesis

Symptoms of an Achilles tendon rupture can vary, but one common and distinctive symptom reported by many individuals is a sudden and audible "popping" or "snapping" sound at the time of injury. This sound is often accompanied by a sharp pain in the back of the leg or ankle. The popping sensation occurs when the Achilles tendon tears or ruptures, and it is caused by the sudden release of tension within the tendon fibers [2].

ARTIGO

The Synergistic Effects of Hyaluronic Acid and Platelet-Rich Plasma for Patellar Chondropathy

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- Márcia da Silva Santos
- Rubens Andrade Martins
- Cláudia Bruno Costa
- Paulo César Hamdan
- Marcos Britto Da Silva
- Gabriel Ohana Marques Azzini
- Luyddy Pires
- Zartur Menegassi
- Gabriel Silva Santos
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biomedicines

MDPI

Review

The Synergistic Effects of Hyaluronic Acid and Platelet-Rich Plasma for Patellar Chondropathy

Fábio Ramos Costa [1], Márcia da Silva Santos [2], Rubens Andrade Martins [3], Cláudia Bruno Costa [1], Paulo César Hamdan [4], Marcos Britto Da Silva [4], Gabriel Ohana Marques Azzini [5,6], Luyddy Pires [5,6], Zartur Menegassi [4], Gabriel Silva Santos [5,6,*] and José Fábio Lana [5,6,7,8]

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Abstract: Musculoskeletal disorders are increasingly prevalent worldwide, causing significant socioeconomic burdens and diminished quality of life. Notably, patellar chondropathy (PC) is among the most widespread conditions affecting joint structures, resulting in profound pain and disability. Hyaluronic acid (HA) and platelet-rich plasma (PRP) have emerged as reliable, effective, and minimally invasive alternatives. Continuous research spanning from laboratory settings to clinical applications demonstrates the numerous advantages of both products. These encompass lubrication, anti-inflammation, and stimulation of cellular behaviors linked to proliferation, differentiation, migration, and the release of essential growth factors. Cumulatively, these benefits support the rejuvenation of bone and cartilaginous tissues, which are otherwise compromised due to the prevailing degenerative and inflammatory responses characteristic of tissue damage. While existing literature delves into the physical, mechanical, and biological facets of these products, as well as their commercial variants and distinct clinical uses, there is limited discussion on their interconnected roles. We explore basic science concepts, product variations, and clinical strategies. This comprehensive examination provides physicians with an alternative insight into the pathophysiology of PC as well as biological mechanisms stimulated by both HA and PRP that contribute to tissue restoration.

Keywords: hyaluronic acid; platelet-rich plasma; patellar chondropathy; regenerative medicine; orthopedics

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Citation: Costa, F.R.; Santos, M.d.S.; Martins, R.A.; Costa, C.B.; Hamdan, P.C.; Da Silva, M.B.; Azzini, G.O.M.; Pires, L.; Menegassi, Z.; Santos, G.S.; et al. The Synergistic Effects of Hyaluronic Acid and Platelet-Rich Plasma for Patellar Chondropathy. *Biomedicines* **2024**, *12*, 6. https://doi.org/10.3390/biomedicines12010006

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1. Introduction

Patellar chondropathy (PC), also referred to informally as "runner's knee", is an orthopedic condition characterized by visible radiological alterations in patellar cartilage and pain in the anterior aspect of the knee [1]. This condition commonly affects younger individuals, and the initial changes include swelling, edema, and cartilage softening (Figure 1). Notorious factors that contribute to PC are trauma, patellofemoral instability, bony anatomic variations, cartilage vulnerability, abnormal patellar kinematics, or occupational hazards [1].

Although sometimes reversible [1,2], depending on the disease stage (Table 1), PC may progress into patellofemoral osteoarthritis (OA) if left untreated [1]. Significant

Produções Científicas

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ARTIGO

Conservative Treatment Approach of Achilles Tendon Ruptures with Orthobiologics: Case Series

- Napoliane Santos
- Luyddy Pires
- Carlos Stéfano
- Alexandre Ribeiro
- Gabriel Silva Santos
- Francisco Honorio
- Lucas Furtado da Fonseca
- Rafael Barnabe Domingues
- Raffael Marum Bachir
- Caroline Kavalco
- Rodrigo Vicente
- Palmerindo Mendonça
- **João Vitor Lana**
- José Fábio Lana

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Santos, et al. J Regen Med Med 2024, 13:1

Journal of Regenerative Medicine

Case Series — A SCITECHNOL JOURNAL

Conservative Treatment Approach of Achilles Tendon Ruptures with Orthobiologics: Case Series

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Abstract

The Achilles Tendon (AT) is one of the strongest tendons in the body; it is also the most frequently ruptured tendon with increasing incidence. Unlike other tendons, AT ruptures are highly correlated with physical activity. In fact, more than 75% of AT ruptures occur during sportive maneuvers. AT rupture is a prevalent and debilitating condition linked to overuse injuries in the ankle and foot. Managing this condition is often complex due to the inadequate vascularity of tendons, relying on synovial fluid diffusion for nutrient supply. The weakened strength resulting from AT rupture can heighten the risk of further complications. While surgical interventions are commonly employed as the primary treatment, challenges may persist in the postoperative period. In contrast, therapeutic interventions with orthobiologics and shockwave therapy have demonstrated notable success in regenerative procedures. In this case series, 3 patients received multiple sessions of bone marrow aspirate, injectable platelet-rich fibrin and extracorporeal shockwave therapy. In the initial sessions, they already exhibited satisfactory healing results as assessed through functional measures, MRI findings, and pain scores. The patients successfully resumed sports activities without complaints, and follow-up MRI scans indicated evident signs of AT restoration. This case series highlights the safe and effective use of autologous orthobiologic products and shockwave therapy as viable alternatives for enhancing the healing process in musculoskeletal tissue injuries.

Methods: Patients received the following treatments: a single Bone Marrow Aspirate (BMA) and then Injectable Platelet-Rich Fibrin (i-PRF) injections fortnightly for 12 weeks, in addition to a weekly session of Extracorporeal Shock Wave Therapy (ESWT). The patients were reassessed at all follow-ups with physical evaluation and ultrasound examination. In addition, we also recommended lifestyle adjustments emphasizing the importance of sleep, diet and metabolism for better tissue recovery. At the end of 12 weeks, we requested a new magnetic resonance imaging of the left ankle for a comparative study, which revealed a significant improvement in the radiological findings. The results of this case report suggest that the application of orthobiologics plus ESWT expedites healing and rehabilitation time and reduces costs and risks inherent to the surgical procedure, which is particularly important in elderly patients and/or with co –morbidities. This approach may therefore represent a viable alternative for the accelerated recovery of musculoskeletal tissue injuries with safety and efficacy.

Keywords

Case Series; Achilles Tendon; Bone Marrow Aspirate; Platelet-Rich Fibrin; Shockwave Therapy; Regenerative Medicine.

Introduction

The Achilles tendon is an important lower limb structure that assists in plantar flexion of the ankle, thus being one of the strongest tendons yet highly susceptible to injuries. It is formed by the congruence of the tendons of the medial and lateral gastrocnemius and soleus muscles, inserting into the posterior surface of the calcaneus [1].

Between the origin and insertion of the tendons that make up the calcaneus, the fibers rotate 90°, so the fibers of the gastrocnemius insert laterally, and those of the soleus medially [2]. In the topography of this rotation of tendon fibers, the most vulnerable area of the tendon is found, around 2 to 6 cm from its insertion in the calcaneus, where blood supply is deficient [3].

The AT may undergo biomechanical (degenerative) or biochemical (inflammatory) changes [4]. AT disorders are more common in individuals who participate in endurance sports that involve repetitive loading of the foot. The rising incidence of ruptures is related to an increase in the participation of the population in recreational and competitive sports and is therefore one of the most common orthopedic disorders in sports medicine [5].

Acute rupture is primarily related to sudden forced plantar flexion during weight bearing with the knee fully extended. Therefore, athletes who play sports that require explosive acceleration, sudden changes in direction or jumping and running are at greater risk [5,6]. Patients with an AT rupture usually describe a history of severe,

SciTechnol

ARTIGO

The role of orthobiologics in chronic wound healing

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- Caroline Mayara Kavalco
- Carolina Caliari
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- Lucas Furtado da Fonseca
- Fabio Ramos Costa
- Andreza da Cruz Silva Reis
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- **José Fábio Lana**

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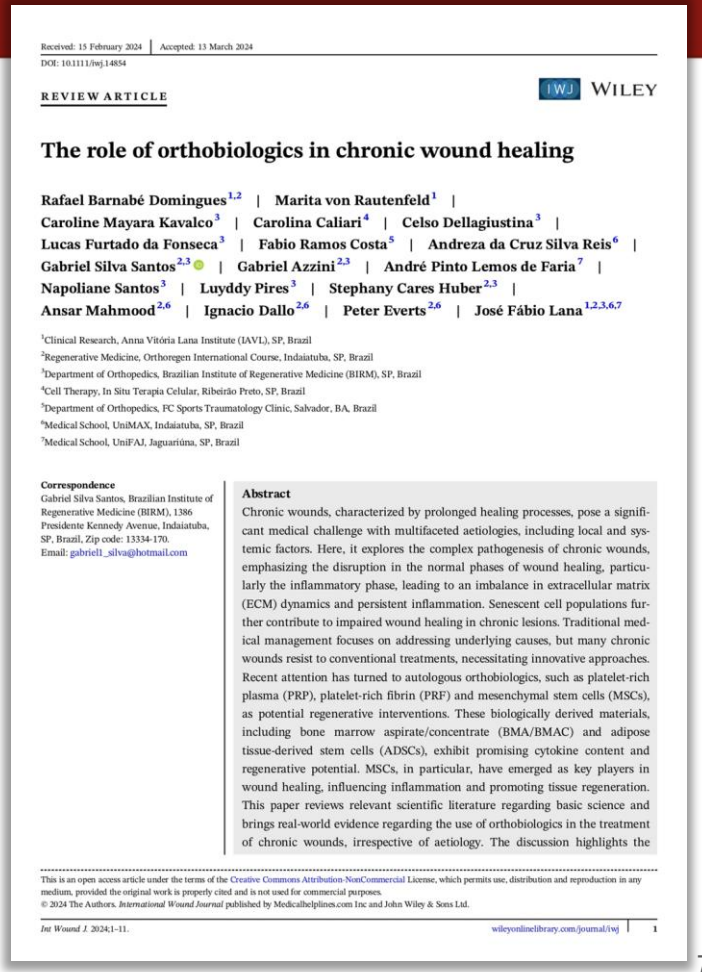

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REVIEW ARTICLE

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The role of orthobiologics in chronic wound healing

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Abstract

Chronic wounds, characterized by prolonged healing processes, pose a significant medical challenge with multifaceted aetiologies, including local and systemic factors. Here, it explores the complex pathogenesis of chronic wounds, emphasizing the disruption in the normal phases of wound healing, particularly the inflammatory phase, leading to an imbalance in extracellular matrix (ECM) dynamics and persistent inflammation. Senescent cell populations further contribute to impaired wound healing in chronic lesions. Traditional medical management focuses on addressing underlying causes, but many chronic wounds resist to conventional treatments, necessitating innovative approaches. Recent attention has turned to autologous orthobiologics, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF) and mesenchymal stem cells (MSCs), as potential regenerative interventions. These biologically derived materials, including bone marrow aspirate/concentrate (BMA/BMAC) and adipose tissue-derived stem cells (ADSCs), exhibit promising cytokine content and regenerative potential. MSCs, in particular, have emerged as key players in wound healing, influencing inflammation and promoting tissue regeneration. This paper reviews relevant scientific literature regarding basic science and brings real-world evidence regarding the use of orthobiologics in the treatment of chronic wounds, irrespective of aetiology. The discussion highlights the

ARTIGO

Sacral Bioneuromodulation: The Role of Bone Marrow Aspirate in Spinal Cord Injuries

- **José Fábio Lana**
- Annu Navani
- Madhan Jeyaraman
- Napoliane Santos
- Luyddy Pires
- Gabriel Silva Santos
- Izair Jefthé Rodrigues
- Douglas Santos
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- Gabriel Azzini
- Lucas Furtado da Fonseca
- Alex Pontes de Macedo
- Stephany Cares Huber
- Daniel de Moraes Ferreira Jorge
- Joseph Purita

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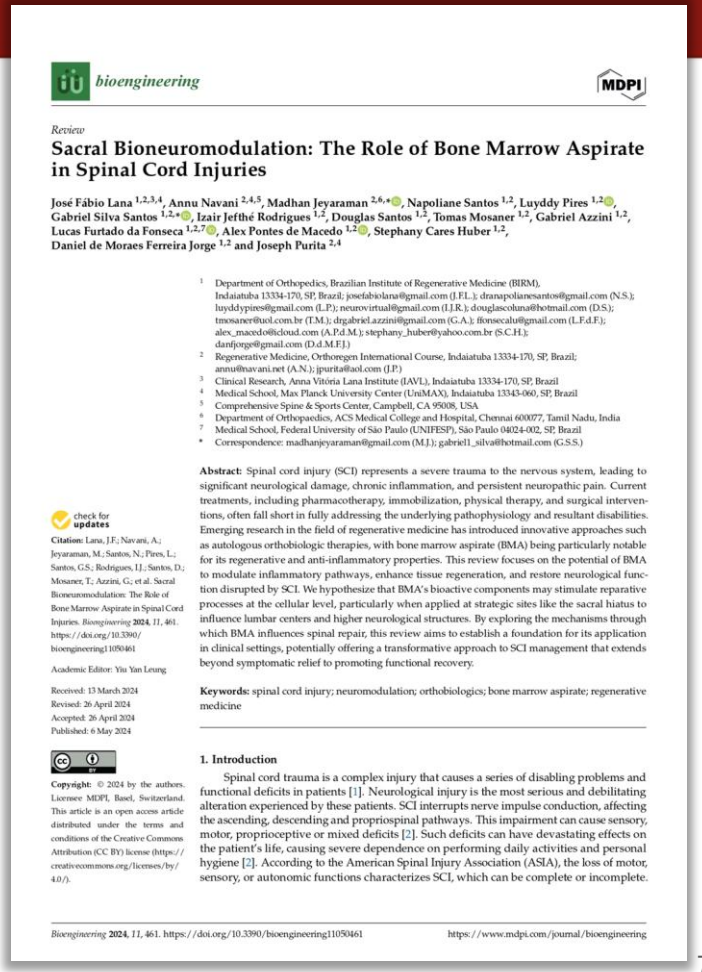

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Review

Sacral Bioneuromodulation: The Role of Bone Marrow Aspirate in Spinal Cord Injuries

José Fábio Lana [1,2,3,4], Annu Navani [2,4,5], Madhan Jeyaraman [2,6,*], Napoliane Santos [1,2], Luyddy Pires [1,2], Gabriel Silva Santos [1,2,*], Izair Jefthé Rodrigues [1,2], Douglas Santos [1,2], Tomas Mosaner [1,2], Gabriel Azzini [1,2], Lucas Furtado da Fonseca [1,2,7], Alex Pontes de Macedo [1,2], Stephany Cares Huber [1,2], Daniel de Moraes Ferreira Jorge [1,2] and Joseph Purita [2,4]

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Abstract: Spinal cord injury (SCI) represents a severe trauma to the nervous system, leading to significant neurological damage, chronic inflammation, and persistent neuropathic pain. Current treatments, including pharmacotherapy, immobilization, physical therapy, and surgical interventions, often fall short in fully addressing the underlying pathophysiology and resultant disabilities. Emerging research in the field of regenerative medicine has introduced innovative approaches such as autologous orthobiologic therapies, with bone marrow aspirate (BMA) being particularly notable for its regenerative and anti-inflammatory properties. This review focuses on the potential of BMA to modulate inflammatory pathways, enhance tissue regeneration, and restore neurological function disrupted by SCI. We hypothesize that BMA's bioactive components may stimulate reparative processes at the cellular level, particularly when applied at strategic sites like the sacral hiatus to influence lumbar centers and higher neurological structures. By exploring the mechanisms through which BMA influences spinal repair, this review aims to establish a foundation for its application in clinical settings, potentially offering a transformative approach to SCI management that extends beyond symptomatic relief to promoting functional recovery.

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Citation: Lana, J.F.; Navani, A.; Jeyaraman, M.; Santos, N.; Pires, L.; Santos, G.S.; Rodrigues, I.J.; Santos, D.; Mosaner, T.; Azzini, G.; et al. Sacral Bioneuromodulation: The Role of Bone Marrow Aspirate in Spinal Cord Injuries. *Bioengineering* **2024**, *11*, 461. https://doi.org/10.3390/bioengineering11050461

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Keywords: spinal cord injury; neuromodulation; orthobiologics; bone marrow aspirate; regenerative medicine

1. Introduction

Spinal cord trauma is a complex injury that causes a series of disabling problems and functional deficits in patients [1]. Neurological injury is the most serious and debilitating alteration experienced by these patients. SCI interrupts nerve impulse conduction, affecting the ascending, descending and propriospinal pathways. This impairment can cause sensory, motor, proprioceptive or mixed deficits [2]. Such deficits can have devastating effects on the patient's life, causing severe dependence on performing daily activities and personal hygiene [2]. According to the American Spinal Injury Association (ASIA), the loss of motor, sensory, or autonomic functions characterizes SCI, which can be complete or incomplete.

ARTIGO

The Biological Role of Platelet Derivatives in Regenerative Aesthetics

- Lorena Cristina Santos
- Giselle Lobo Lana
- Gabriel Silva Santos
- Silvia Beatriz Coutinho Visoni
- Rayssa Junqueira Brigagão
- Napoliane Santos
- Rafaela Sobreiro
- Andreza da Cruz Silva Reis
- Bruno Lima Rodrigues
- Sabrina Ferrari
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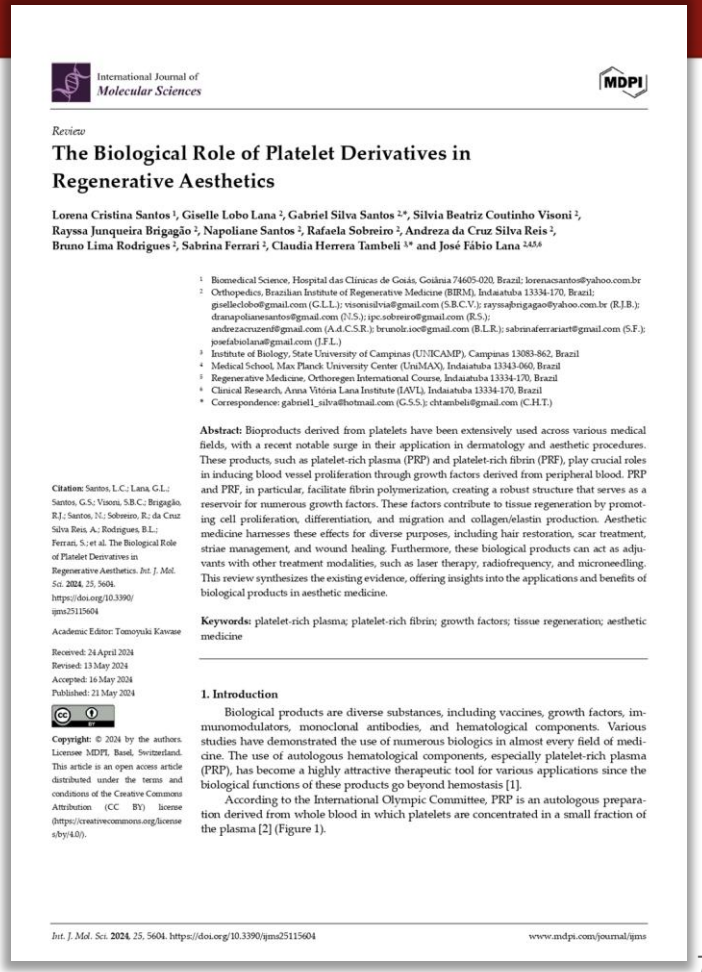

International Journal of Molecular Sciences

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Review

The Biological Role of Platelet Derivatives in Regenerative Aesthetics

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Abstract: Bioproducts derived from platelets have been extensively used across various medical fields, with a recent notable surge in their application in dermatology and aesthetic procedures. These products, such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), play crucial roles in inducing blood vessel proliferation through growth factors derived from peripheral blood. PRP and PRF, in particular, facilitate fibrin polymerization, creating a robust structure that serves as a reservoir for numerous growth factors. These factors contribute to tissue regeneration by promoting cell proliferation, differentiation, and migration and collagen/elastin production. Aesthetic medicine harnesses these effects for diverse purposes, including hair restoration, scar treatment, striae management, and wound healing. Furthermore, these biological products can act as adjuvants with other treatment modalities, such as laser therapy, radiofrequency, and microneedling. This review synthesizes the existing evidence, offering insights into the applications and benefits of biological products in aesthetic medicine.

Keywords: platelet-rich plasma; platelet-rich fibrin; growth factors; tissue regeneration; aesthetic medicine

1. Introduction

Biological products are diverse substances, including vaccines, growth factors, immunomodulators, monoclonal antibodies, and hematological components. Various studies have demonstrated the use of numerous biologics in almost every field of medicine. The use of autologous hematological components, especially platelet-rich plasma (PRP), has become a highly attractive therapeutic tool for various applications since the biological functions of these products go beyond hemostasis [1].

According to the International Olympic Committee, PRP is an autologous preparation derived from whole blood in which platelets are concentrated in a small fraction of the plasma [2] (Figure 1).

ARTIGO

Orthobiologic Management Options for Degenerative Disc Disease

- Cezar Augusto Alves de Oliveira
- Bernardo Scaldini Oliveira
- Rafael Theodoro
- Joshua Wang
- Gabriel Silva Santos
- Bruno Lima Rodrigues
- Izair Jefthé Rodrigues
- Daniel de Moraes Ferreira Jorge
- Madhan Jeyaraman
- Peter Albert Everts
- Annu Navani
- **José Fábio Lana**

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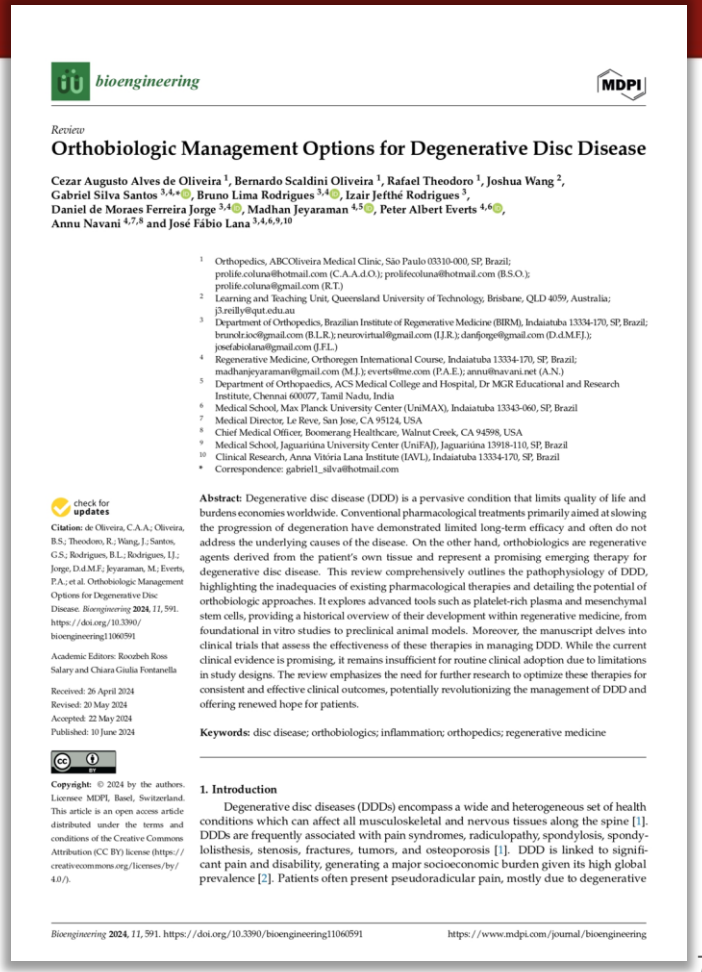

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Review

Orthobiologic Management Options for Degenerative Disc Disease

Cezar Augusto Alves de Oliveira [1], Bernardo Scaldini Oliveira [1], Rafael Theodoro [1], Joshua Wang [2], Gabriel Silva Santos [3,4,*], Bruno Lima Rodrigues [3,4], Izair Jefthé Rodrigues [3], Daniel de Moraes Ferreira Jorge [3,4], Madhan Jeyaraman [4,5], Peter Albert Everts [4,6], Annu Navani [4,7,8] and José Fábio Lana [3,4,6,9,10]

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Abstract: Degenerative disc disease (DDD) is a pervasive condition that limits quality of life and burdens economies worldwide. Conventional pharmacological treatments primarily aimed at slowing the progression of degeneration have demonstrated limited long-term efficacy and often do not address the underlying causes of the disease. On the other hand, orthobiologics are regenerative agents derived from the patient's own tissue and represent a promising emerging therapy for degenerative disc disease. This review comprehensively outlines the pathophysiology of DDD, highlighting the inadequacies of existing pharmacological therapies and detailing the potential of orthobiologic approaches. It explores advanced tools such as platelet-rich plasma and mesenchymal stem cells, providing a historical overview of their development within regenerative medicine, from foundational in vitro studies to preclinical animal models. Moreover, the manuscript delves into clinical trials that assess the effectiveness of these therapies in managing DDD. While the current clinical evidence is promising, it remains insufficient for routine clinical adoption due to limitations in study designs. The review emphasizes the need for further research to optimize these therapies for consistent and effective clinical outcomes, potentially revolutionizing the management of DDD and offering renewed hope for patients.

Keywords: disc disease; orthobiologics; inflammation; orthopedics; regenerative medicine

1. Introduction

Degenerative disc diseases (DDDs) encompass a wide and heterogeneous set of health conditions which can affect all musculoskeletal and nervous tissues along the spine [1]. DDDs are frequently associated with pain syndromes, radiculopathy, spondylosis, spondylolisthesis, stenosis, fractures, tumors, and osteoporosis [1]. DDD is linked to significant pain and disability, generating a major socioeconomic burden given its high global prevalence [2]. Patients often present pseudoradicular pain, mostly due to degenerative

ARTIGO

Profound Properties of Protein-Rich, Platelet-Rich Plasma Matrices as Novel, Multi-Purpose Biological Platforms in Tissue Repair, Regeneration, and Wound Healing

- Peter A. Everts
- **José Fábio Lana**
- Robert W. Alexander
- Ignacio Dallo
- Elizaveta Kon
- Mary A. Ambach
- André van Zundert
- Luga Podesta

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Veículo: MDPI – International Journal of Molecular Science

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International Journal of *Molecular Sciences*

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Review

Profound Properties of Protein-Rich, Platelet-Rich Plasma Matrices as Novel, Multi-Purpose Biological Platforms in Tissue Repair, Regeneration, and Wound Healing

Peter A. Everts [1,2,*], José Fábio Lana [2], Robert W. Alexander [3,4], Ignacio Dallo [5], Elizaveta Kon [6,7], Mary A. Ambach [8], André van Zundert [9] and Luga Podesta [10,11]

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Abstract: Autologous platelet-rich plasma (PRP) preparations are prepared at the point of care. Centrifugation cellular density separation sequesters a fresh unit of blood into three main fractions: a platelet-poor plasma (PPP) fraction, a stratum rich in platelets (platelet concentrate), and variable leukocyte bioformulation and erythrocyte fractions. The employment of autologous platelet concentrates facilitates the biological potential to accelerate and support numerous cellular activities that can lead to tissue repair, tissue regeneration, wound healing, and, ultimately, functional and structural repair. Normally, after PRP preparation, the PPP fraction is discarded. One of the less well-known but equally important features of PPP is that particular growth factors (GFs) are not abundantly present in PRP, as they reside outside of the platelet alpha granules. Precisely, insulin-like growth factor-1 (IGF-1) and hepatocyte growth factor (HGF) are mainly present in the PPP fraction. In addition to their roles as angiogenesis activators, these plasma-based GFs are also known to inhibit inflammation and fibrosis, and they promote keratinocyte migration and support tissue repair and wound healing. Additionally, PPP is known for the presence of exosomes and other macrovesicles, exerting cell–cell communication and cell signaling. Newly developed ultrafiltration technologies incorporate PPP processing methods by eliminating, in a fast and efficient manner, plasma water, cytokines, molecules, and plasma proteins with a molecular mass (weight) less than the pore size of the fibers. Consequently, a viable and viscous protein concentrate of functional total proteins, like fibrinogen, albumin, and alpha-2-macroglobulin is created. Consolidating a small volume of high platelet concentrate with a small volume of highly concentrated protein-rich PPP creates a protein-rich, platelet-rich plasma (PR-PRP) biological preparation. After the activation of proteins, mainly fibrinogen, the PR-PRP matrix retains and facilitates interactions between invading resident cells, like macrophages, fibroblast, and mesenchymal stem cells (MSCs), as well as the embedded concentrated PRP cells and molecules. The administered PR-PRP biologic will ultimately undergo fibrinolysis, leading to a sustained release of concentrated cells and molecules that have been retained in the PR-PRP matrix until the matrix is dissolved. We will discuss the unique biological and tissue reparative and regenerative properties of the PR-PRP matrix.

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ARTIGO

Nebulized Glutathione as a Key Antioxidant for the Treatment of Oxidative Stress in Neurodegenerative Conditions

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- Alexandre Rios
- Renata Takeyama
- Napoliane Santos
- Luyddy Pires
- Gabriel Silva Santos
- Izair Jefthé Rodrigues
- Madhan Jeyaraman
- Joseph Purita
- **José Fábio Lana**

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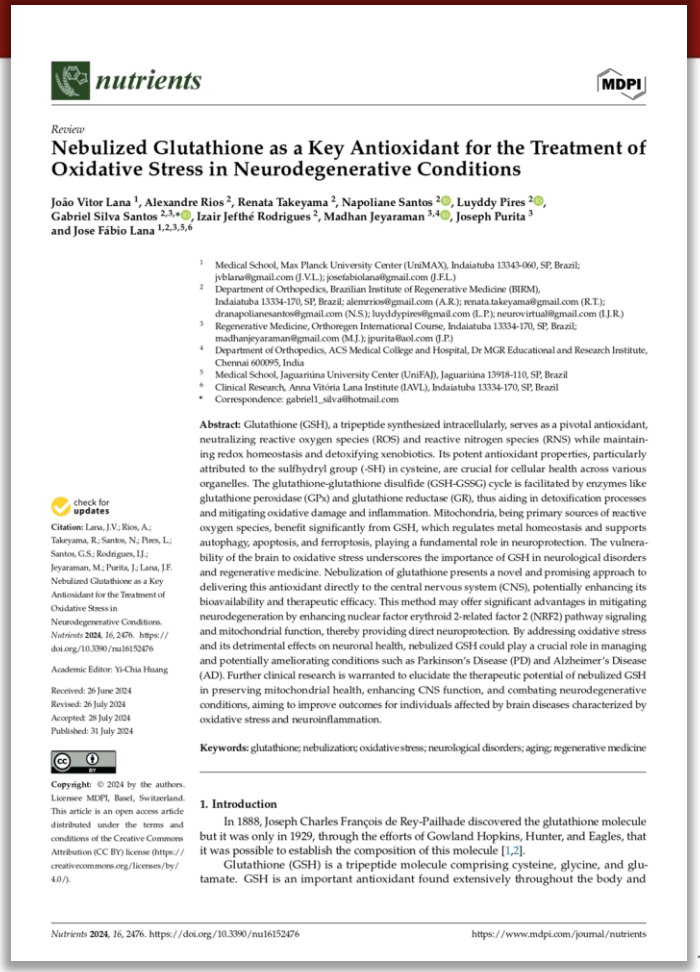

nutrients

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Review

Nebulized Glutathione as a Key Antioxidant for the Treatment of Oxidative Stress in Neurodegenerative Conditions

João Vitor Lana [1], Alexandre Rios [2], Renata Takeyama [2], Napoliane Santos [2], Luyddy Pires [2], Gabriel Silva Santos [2,3,*], Izair Jefthé Rodrigues [2], Madhan Jeyaraman [3,4], Joseph Purita [3] and Jose Fábio Lana [1,2,3,5,6]

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Abstract: Glutathione (GSH), a tripeptide synthesized intracellularly, serves as a pivotal antioxidant, neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS) while maintaining redox homeostasis and detoxifying xenobiotics. Its potent antioxidant properties, particularly attributed to the sulfhydryl group (-SH) in cysteine, are crucial for cellular health across various organelles. The glutathione-glutathione disulfide (GSH-GSSG) cycle is facilitated by enzymes like glutathione peroxidase (GPx) and glutathione reductase (GR), thus aiding in detoxification processes and mitigating oxidative damage and inflammation. Mitochondria, being primary sources of reactive oxygen species, benefit significantly from GSH, which regulates metal homeostasis and supports autophagy, apoptosis, and ferroptosis, playing a fundamental role in neuroprotection. The vulnerability of the brain to oxidative stress underscores the importance of GSH in neurological disorders and regenerative medicine. Nebulization of glutathione presents a novel and promising approach to delivering this antioxidant directly to the central nervous system (CNS), potentially enhancing its bioavailability and therapeutic efficacy. This method may offer significant advantages in mitigating neurodegeneration by enhancing nuclear factor erythroid 2-related factor 2 (NRF2) pathway signaling and mitochondrial function, thereby providing direct neuroprotection. By addressing oxidative stress and its detrimental effects on neuronal health, nebulized GSH could play a crucial role in managing and potentially ameliorating conditions such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Further clinical research is warranted to elucidate the therapeutic potential of nebulized GSH in preserving mitochondrial health, enhancing CNS function, and combating neurodegenerative conditions, aiming to improve outcomes for individuals affected by brain diseases characterized by oxidative stress and neuroinflammation.

Keywords: glutathione; nebulization; oxidative stress; neurological disorders; aging; regenerative medicine

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Citation: Lana, J.V.; Rios, A.; Takeyama, R.; Santos, N.; Pires, L.; Santos, G.S.; Rodrigues, I.J.; Jeyaraman, M.; Purita, J.; Lana, J.F. Nebulized Glutathione as a Key Antioxidant for the Treatment of Oxidative Stress in Neurodegenerative Conditions. *Nutrients* **2024**, *16*, 2476. https://doi.org/10.3390/nu16152476

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1. Introduction

In 1888, Joseph Charles François de Rey-Pailhade discovered the glutathione molecule but it was only in 1929, through the efforts of Gowland Hopkins, Hunter, and Eagles, that it was possible to establish the composition of this molecule [1,2].

Glutathione (GSH) is a tripeptide molecule comprising cysteine, glycine, and glutamate. GSH is an important antioxidant found extensively throughout the body and

ARTIGO

ViSCNOVAS: A Novel Classification System for Hyaluronic Acid-Based Gels in Orthobiologic Products and Regenerative Medicine

- Fábio Ramos Costa
- Luyddy Pires
- Rubens Andrade Martins
- Bruno Ramos Costa
- Gabriel Silva Santos
- **José Fábio Lana**

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Veículo: MDPI - Gels

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gels

MDPI

Communication

ViSCNOVAS: A Novel Classification System for Hyaluronic Acid-Based Gels in Orthobiologic Products and Regenerative Medicine

Fábio Ramos Costa [1], Luyddy Pires [2,3], Rubens Andrade Martins [4], Bruno Ramos Costa [5], Gabriel Silva Santos [2,3,*] and José Fábio Lana [2,3,6,7,8]

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Abstract: Hyaluronic acid (HA), a naturally occurring polysaccharide, holds immense potential in regenerative medicine due to its diverse biological functions and clinical applications, particularly in gel formulations. This paper presents a comprehensive exploration of HA, encompassing its origins, molecular characteristics, and therapeutic roles in gel-based interventions. Initially identified in bovine vitreous humor, HA has since been found in various tissues and fluids across vertebrate organisms and bacterial sources, exhibiting consistent physicochemical properties. The synthesis of HA by diverse cell types underscores its integral role in the extracellular matrix and its relevance to tissue homeostasis and repair. Clinical applications of HA, particularly in addressing musculoskeletal ailments such as osteoarthritis, are examined, highlighting its efficacy and safety in promoting tissue regeneration and pain relief. Building upon this foundation, a novel classification system for HA-based interventions is proposed, aiming to standardize treatment protocols and optimize patient outcomes. The ViSCNOVAS classification system refers to viscosity, storage, chain, number, origin, volume, amount, and size. This classification is specifically designed for HA-based orthobiologic products used in regenerative medicine, including orthopedics, sports medicine, aesthetics, cosmetic dermatology, and wound healing. It aims to provide clinicians with a structured framework for personalized treatment strategies. Future directions in HA research are also discussed, emphasizing the need for further validation and refinement of the proposed classification system to advance the field of regenerative medicine. Overall, this manuscript elucidates the biological functions of hyaluronic acid and its potential in clinical practice while advocating for standardization to enhance patient care in various regenerative applications.

Keywords: hyaluronic acid; orthobiologics; classification; regenerative medicine; clinical applications

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1. Introduction

Hyaluronic acid (HA), often referred to as hyaluronan, is a naturally occurring biological compound found in numerous tissues and fluids within the body [1]. Notably, HA possesses unique gel-forming properties, making it a crucial component in various medical and cosmetic applications. These properties enable HA to form hydrogels that exhibit excellent biocompatibility, viscoelasticity, and water retention capabilities, which are essential for its role in regenerative medicine.. It can be obtained from various sources,

ARTIGO

Preparing the soil: Adjusting the metabolic health of patients with chronic wounds and musculoskeletal diseases

- Lucas Furtado da Fonseca
- Gabriel Silva Santos
- Gabriel Azzini
- Tomas Mosaner
- Daniel de Moraes Ferreira Jorge
- Alex Pontes de Macedo
- Stephany Cares Huber
- Pablo Sobreiro
- Ignacio Dallo
- Madhan Jeyaraman
- Peter Albert Everts
- Annu Navani
- **José Fábio Lana**

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Veículo: IWJ - WILEY

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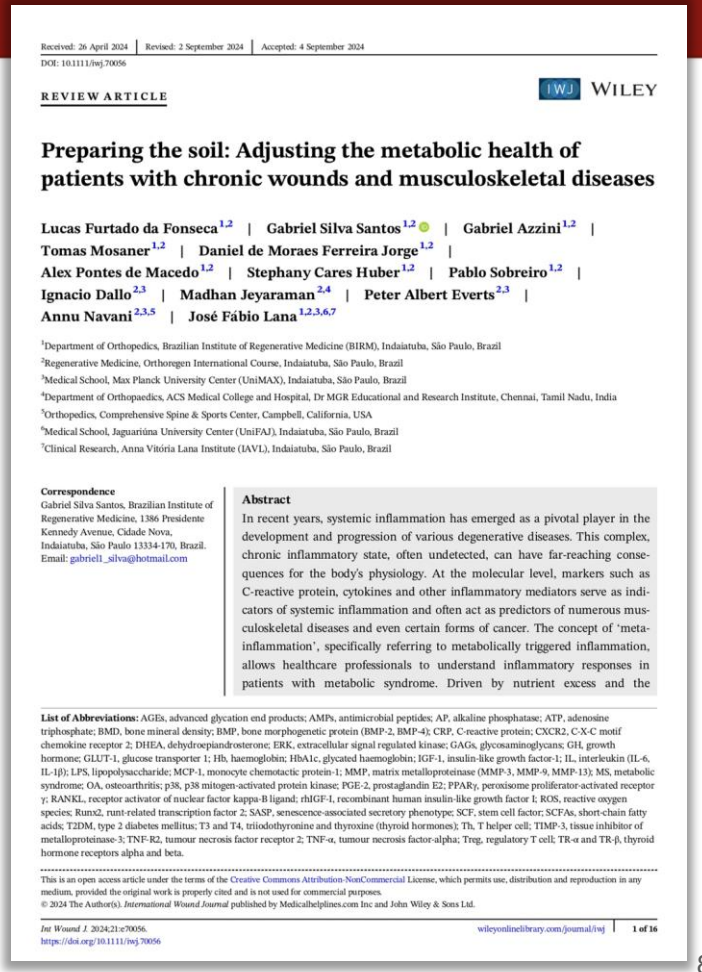

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REVIEW ARTICLE

IWJ WILEY

Preparing the soil: Adjusting the metabolic health of patients with chronic wounds and musculoskeletal diseases

Lucas Furtado da Fonseca[1,2] | Gabriel Silva Santos[1,2] | Gabriel Azzini[1,2] | Tomas Mosaner[1,2] | Daniel de Moraes Ferreira Jorge[1,2] | Alex Pontes de Macedo[1,2] | Stephany Cares Huber[1,2] | Pablo Sobreiro[1,2] | Ignacio Dallo[2,3] | Madhan Jeyaraman[2,4] | Peter Albert Everts[2,3] | Annu Navani[2,3,5] | José Fábio Lana[1,2,3,6,7]

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Abstract

In recent years, systemic inflammation has emerged as a pivotal player in the development and progression of various degenerative diseases. This complex, chronic inflammatory state, often undetected, can have far-reaching consequences for the body's physiology. At the molecular level, markers such as C-reactive protein, cytokines and other inflammatory mediators serve as indicators of systemic inflammation and often act as predictors of numerous musculoskeletal diseases and even certain forms of cancer. The concept of 'meta-inflammation', specifically referring to metabolically triggered inflammation, allows healthcare professionals to understand inflammatory responses in patients with metabolic syndrome. Driven by nutrient excess and the

List of Abbreviations: AGEs, advanced glycation end products; AMPs, antimicrobial peptides; AP, alkaline phosphatase; ATP, adenosine triphosphate; BMD, bone mineral density; BMP, bone morphogenetic protein (BMP-2, BMP-4); CRP, C-reactive protein; CXCR2, C-X-C motif chemokine receptor 2; DHEA, dehydroepiandrosterone; ERK, extracellular signal regulated kinase; GAGs, glycosaminoglycans; GH, growth hormone; GLUT-1, glucose transporter 1; Hb, haemoglobin; HbA1c, glycated haemoglobin; IGF-1, insulin-like growth factor-1; IL, interleukin (IL-6, IL-1β); LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase (MMP-3, MMP-9, MMP-13); MS, metabolic syndrome; OA, osteoarthritis; p38, p38 mitogen-activated protein kinase; PGE-2, prostaglandin E2; PPARγ, peroxisome proliferator-activated receptor γ; RANKL, receptor activator of nuclear factor kappa-B ligand; rhIGF-1, recombinant human insulin-like growth factor I; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SASP, senescence-associated secretory phenotype; SCF, stem cell factor; SCFAs, short-chain fatty acids; T2DM, type 2 diabetes mellitus; T3 and T4, triiodothyronine and thyroxine (thyroid hormones); Th, T helper cell; TIMP-3, tissue inhibitor of metalloproteinase-3; TNF-R2, tumour necrosis factor receptor 2; TNF-α, tumour necrosis factor-alpha; Treg, regulatory T cell; TR-α and TR-β, thyroid hormone receptors alpha and beta.

ARTIGO

Evolution and Innovations in Bone Marrow Cellular Therapy for Musculoskeletal Disorders: Tracing the Historical Trajectory and Contemporary Advances

- José Fábio Lana
- Gabriela Caponero de Brito
- André Kruel
- Benjamim Brito
- Gabriel Silva Santos
- Carolina Caliari
- Francesca Salamanna
- Maria Sartori
- Giovanni Barbanti Brodano
- Fábio Ramos Costa
- Madhan Jeyaraman
- Ignácio Dallo
- Pedro Bernaldez
- Joseph Purita
- Marco Antonio Percope de Andrade
- Peter Albert Everts

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Veículo: MDPI - Bioengineering

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Review

Evolution and Innovations in Bone Marrow Cellular Therapy for Musculoskeletal Disorders: Tracing the Historical Trajectory and Contemporary Advances

José Fábio Lana [1,2,34,5], Gabriela Caponero de Brito [1], André Kruel [1], Benjamim Brito [1], Gabriel Silva Santos [1,*], Carolina Caliari [6], Francesca Salamanna [7], Maria Sartori [7], Giovanni Barbanti Brodano [8], Fábio Ramos Costa [9], Madhan Jeyaraman [10,11,12], Ignácio Dallo [2,3,13], Pedro Bernaldez [13], Joseph Purita [2,3], Marco Antonio Percope de Andrade [14] and Peter Albert Everts [2,3,15]

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Abstract: Bone marrow cellular therapy has undergone a remarkable evolution, significantly impacting the treatment of musculoskeletal disorders. This review traces the historical trajectory from early mythological references to contemporary scientific advancements. The groundbreaking work of Friedenstein in 1968, identifying fibroblast colony-forming cells in bone marrow, laid the foundation for future studies. Caplan's subsequent identification of mesenchymal stem cells (MSCs) in 1991 highlighted their differentiation potential and immunomodulatory properties, establishing them as key players in regenerative medicine. Contemporary research has focused on refining techniques for isolating and applying bone marrow-derived MSCs. These cells have shown promise in treating conditions like osteonecrosis, osteoarthritis, and tendon injuries thanks to their ability to promote tissue repair, modulate immune responses, and enhance angiogenesis. Clinical studies have demonstrated significant improvements in pain relief, functional recovery, and tissue regeneration. Innovations such as the ACH classification system and advancements in bone marrow aspiration methods have standardized practices, improving the consistency and efficacy of these therapies. Recent clinical trials have validated the therapeutic potential of bone marrow-derived products, highlighting their advantages in both surgical and non-surgical applications. Studies have shown that MSCs can reduce inflammation, support bone healing, and enhance cartilage repair. However, challenges remain, including the need for rigorous characterization of

ARTIGO

SDIMMMER: A Proposed Clinical Approach to Optimize Cellular Physiology in Regenerative Medicine

- **João Vitor Lana**
- José Fábio Lana
- Gregory Melo
- Gabriel Ohana Marques Azzini
- Gabriel Silva Santos
- Tomas Mosaner
- Daniel de Moraes Ferreira Jorge
- Lucas Furtado da Fonseca
- André Kruel
- Fábio Ramos Costa
- Madhan Jeyaraman
- Alex Pontes de Macedo
- Napoliane Santos
- Luyddy Pires
- Claudia Herrera Tambeli

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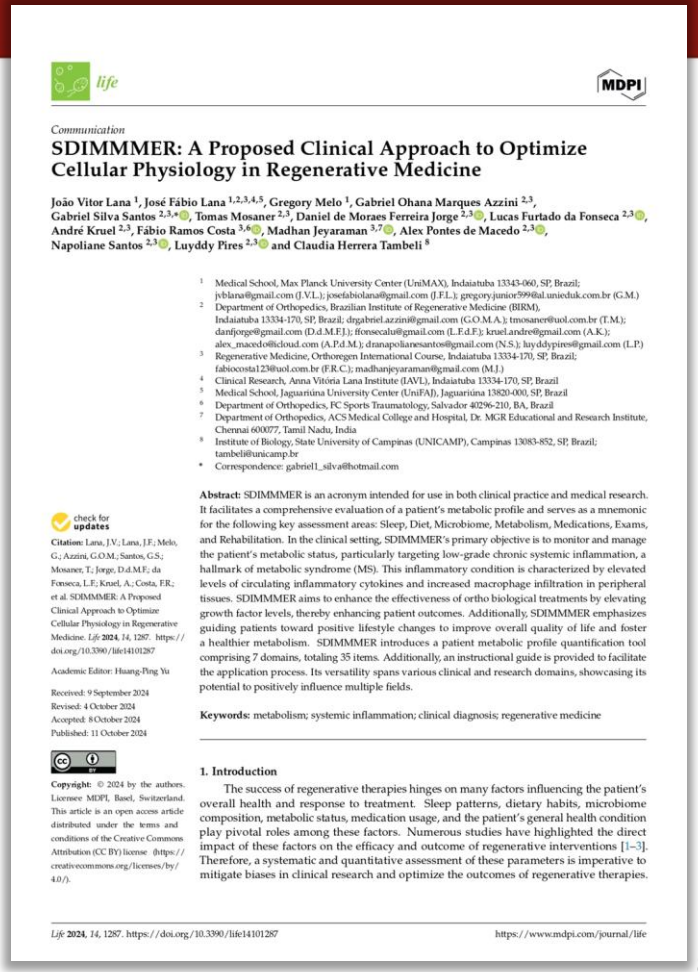

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Communication

SDIMMMER: A Proposed Clinical Approach to Optimize Cellular Physiology in Regenerative Medicine

João Vitor Lana [1], José Fábio Lana [1,2,3,4,5], Gregory Melo [1], Gabriel Ohana Marques Azzini [2,3], Gabriel Silva Santos [2,3,*], Tomas Mosaner [2,3], Daniel de Moraes Ferreira Jorge [2,3], Lucas Furtado da Fonseca [2,3], André Kruel [2,3], Fábio Ramos Costa [3,6], Madhan Jeyaraman [3,7], Alex Pontes de Macedo [2,3], Napoliane Santos [2,3], Luyddy Pires [2,3] and Claudia Herrera Tambeli [8]

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Abstract: SDIMMMER is an acronym intended for use in both clinical practice and medical research. It facilitates a comprehensive evaluation of a patient's metabolic profile and serves as a mnemonic for the following key assessment areas: Sleep, Diet, Microbiome, Metabolism, Medications, Exams, and Rehabilitation. In the clinical setting, SDIMMMER's primary objective is to monitor and manage the patient's metabolic status, particularly targeting low-grade chronic systemic inflammation, a hallmark of metabolic syndrome (MS). This inflammatory condition is characterized by elevated levels of circulating inflammatory cytokines and increased macrophage infiltration in peripheral tissues. SDIMMMER aims to enhance the effectiveness of ortho biological treatments by elevating growth factor levels, thereby enhancing patient outcomes. Additionally, SDIMMMER emphasizes guiding patients toward positive lifestyle changes to improve overall quality of life and foster a healthier metabolism. SDIMMMER introduces a patient metabolic profile quantification tool comprising 7 domains, totaling 35 items. Additionally, an instructional guide is provided to facilitate the application process. Its versatility spans various clinical and research domains, showcasing its potential to positively influence multiple fields.

Keywords: metabolism; systemic inflammation; clinical diagnosis; regenerative medicine

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1. Introduction

The success of regenerative therapies hinges on many factors influencing the patient's overall health and response to treatment. Sleep patterns, dietary habits, microbiome composition, metabolic status, medication usage, and the patient's general health condition play pivotal roles among these factors. Numerous studies have highlighted the direct impact of these factors on the efficacy and outcome of regenerative interventions [1–3]. Therefore, a systematic and quantitative assessment of these parameters is imperative to mitigate biases in clinical research and optimize the outcomes of regenerative therapies.

ARTIGO

Regenerative Inflammation: The Mechanism Explained from the Perspective of Buffy-Coat Protagonism and Macrophage Polarization

- Rubens Andrade Martins
- Fábio Ramos Costa
- Luyddy Pires
- Márcia Santos
- Gabriel Silva Santos
- João Vitor Lana
- Bruno Ramos Costa
- Napoliane Santos
- Alex Pontes de Macedo
- André Krue
- **José Fábio Lana**

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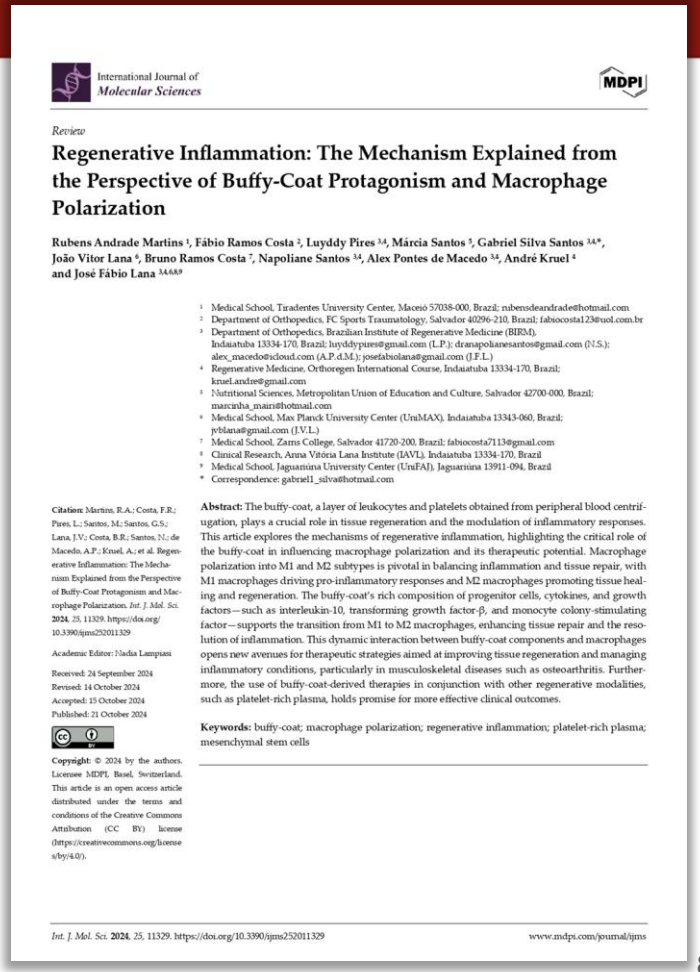

International Journal of Molecular Sciences

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Review

Regenerative Inflammation: The Mechanism Explained from the Perspective of Buffy-Coat Protagonism and Macrophage Polarization

Rubens Andrade Martins [1], Fábio Ramos Costa [2], Luyddy Pires [3,4], Márcia Santos [5], Gabriel Silva Santos [3,4,*], João Vitor Lana [6], Bruno Ramos Costa [7], Napoliane Santos [3,4], Alex Pontes de Macedo [3,4], André Kruel [4] and José Fábio Lana [3,4,6,8,9]

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Abstract: The buffy-coat, a layer of leukocytes and platelets obtained from peripheral blood centrifugation, plays a crucial role in tissue regeneration and the modulation of inflammatory responses. This article explores the mechanisms of regenerative inflammation, highlighting the critical role of the buffy-coat in influencing macrophage polarization and its therapeutic potential. Macrophage polarization into M1 and M2 subtypes is pivotal in balancing inflammation and tissue repair, with M1 macrophages driving pro-inflammatory responses and M2 macrophages promoting tissue healing and regeneration. The buffy-coat's rich composition of progenitor cells, cytokines, and growth factors—such as interleukin-10, transforming growth factor-β, and monocyte colony-stimulating factor—supports the transition from M1 to M2 macrophages, enhancing tissue repair and the resolution of inflammation. This dynamic interaction between buffy-coat components and macrophages opens new avenues for therapeutic strategies aimed at improving tissue regeneration and managing inflammatory conditions, particularly in musculoskeletal diseases such as osteoarthritis. Furthermore, the use of buffy-coat-derived therapies in conjunction with other regenerative modalities, such as platelet-rich plasma, holds promise for more effective clinical outcomes.

Keywords: buffy-coat; macrophage polarization; regenerative inflammation; platelet-rich plasma; mesenchymal stem cells

ARTIGO

Upper Crossed Syndrome and Scapulae Upper-Trapping: A Mesotherapy Protocol in Cervicoscapulobrachial Pain —The 8:1 Block

- Luyddy Pires
- Napoliane Santos
- João Vitor Lana
- Alex Pontes de Macedo
- Fábio Ramos Costa
- Gabriel Ohana Marques Azzini
- Tomas Mosaner
- Daniel de Moraes Ferreira Jorge
- Gabriel Silva Santos
- Arthur Medeiros
- José Alexandre Reale Pereira
- **José Fábio Lana**

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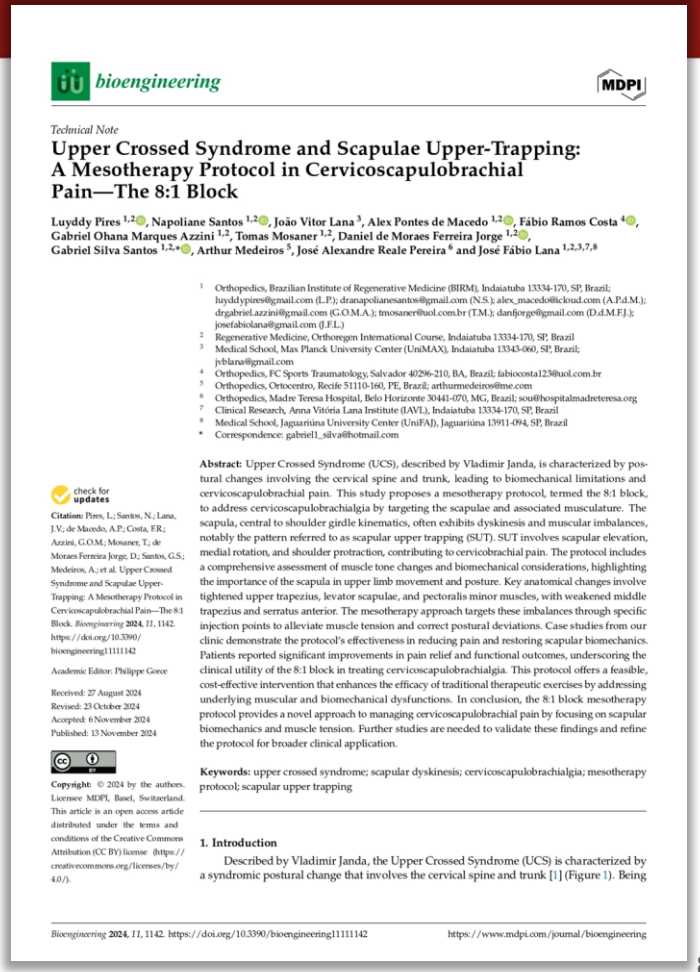

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Technical Note

Upper Crossed Syndrome and Scapulae Upper-Trapping: A Mesotherapy Protocol in Cervicoscapulobrachial Pain—The 8:1 Block

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Citation: Pires, L.; Santos, N.; Lana, J.V.; de Macedo, A.P.; Costa, F.R.; Azzini, G.O.M.; Mosaner, T.; de Moraes Ferreira Jorge, D.; Santos, G.S.; Medeiros, A.; et al. Upper Crossed Syndrome and Scapulae Upper-Trapping: A Mesotherapy Protocol in Cervicoscapulobrachial Pain—The 8:1 Block. *Bioengineering* **2024**, *11*, 1142. https://doi.org/10.3390/bioengineering11111142

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Abstract: Upper Crossed Syndrome (UCS), described by Vladimir Janda, is characterized by postural changes involving the cervical spine and trunk, leading to biomechanical limitations and cervicoscapulobrachial pain. This study proposes a mesotherapy protocol, termed the 8:1 block, to address cervicoscapulobrachialgia by targeting the scapulae and associated musculature. The scapula, central to shoulder girdle kinematics, often exhibits dyskinesis and muscular imbalances, notably the pattern referred to as scapular upper trapping (SUT). SUT involves scapular elevation, medial rotation, and shoulder protraction, contributing to cervicobrachial pain. The protocol includes a comprehensive assessment of muscle tone changes and biomechanical considerations, highlighting the importance of the scapula in upper limb movement and posture. Key anatomical changes involve tightened upper trapezius, levator scapulae, and pectoralis minor muscles, with weakened middle trapezius and serratus anterior. The mesotherapy approach targets these imbalances through specific injection points to alleviate muscle tension and correct postural deviations. Case studies from our clinic demonstrate the protocol's effectiveness in reducing pain and restoring scapular biomechanics. Patients reported significant improvements in pain relief and functional outcomes, underscoring the clinical utility of the 8:1 block in treating cervicoscapulobrachialgia. This protocol offers a feasible, cost-effective intervention that enhances the efficacy of traditional therapeutic exercises by addressing underlying muscular and biomechanical dysfunctions. In conclusion, the 8:1 block mesotherapy protocol provides a novel approach to managing cervicoscapulobrachial pain by focusing on scapular biomechanics and muscle tension. Further studies are needed to validate these findings and refine the protocol for broader clinical application.

Keywords: upper crossed syndrome; scapular dyskinesis; cervicoscapulobrachialgia; mesotherapy protocol; scapular upper trapping

1. Introduction

Described by Vladimir Janda, the Upper Crossed Syndrome (UCS) is characterized by a syndromic postural change that involves the cervical spine and trunk [1] (Figure 1). Being

ARTIGO

Innovative Approaches in Knee Osteoarthritis Treatment: A Comprehensive Review of Bone Marrow-Derived Products

- **José Fábio Lana**
- Joseph Purita
- Madhan Jeyaraman
- Bianca Freitas de Souza
- Bruno Lima Rodrigues
- Stephany Cares Huber
- Carolina Caliari
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- Ignacio Dallo
- Annu Navani
- Marco Antônio Percope De Andrade
- Peter Albert Everts

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Veículo: MDPI - Biomedicines

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Review

Innovative Approaches in Knee Osteoarthritis Treatment: A Comprehensive Review of Bone Marrow-Derived Products

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Abstract: Knee osteoarthritis (OA) is a chronic articular disease characterized by the progressive degeneration of cartilage and bone tissue, leading to the appearance of subchondral cysts, osteophyte formation, and synovial inflammation. Conventional treatments consist of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and glucocorticoids. However, the prolonged use of these drugs causes adverse effects. NSAIDs, for instance, are known to be nephrotoxic, increasing the damage to articular cartilage. New therapies capable of accelerating the process of tissue regeneration and repair are being discussed, such as the use of orthobiologics that are naturally found in the body and obtained through minimally invasive collection and/or laboratory manipulations. Bone marrow aspirate (BMA) and bone marrow aspirate concentrate (BMAC) are both rich in hematopoietic stem cells, mesenchymal stem cells (MSCs), and growth factors (GFs) that can be used in the healing process due to their anabolic and anti-inflammatory effects. The aim of this literature review is to assess the efficacy of BMA and BMAC in the treatment of knee OA based on the favorable results that researchers have obtained with the use of both orthobiologics envisaging an accelerated healing process and the prevention of OA progression.

Keywords: knee osteoarthritis; bone marrow aspirate; bone marrow aspirate concentrate; stem cells; regenerative medicine

1. Introduction

Knee osteoarthritis (KOA) is a disease characterized by the wear of articular cartilage and bone changes and may have several causes and risk factors. Bone sclerosis, capsular fibrosis, and osteophyte formation are the results of tissue growth [1]. KOA involves abnormal remodeling driven by inflammatory mediators within the joint (Figure 1). Pathological changes in KOA include articular cartilage degradation, subchondral bone thickening,

ARTIGO

Gut microbiome and orthopaedic health: Bridging the divide between digestion and bone integrity

- Naveen Jeyaraman
- Madhan Jeyaraman
- Priya Dhanpal
- Swaminathan Ramasubramanian
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- Gabriel Silva Santos
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MINIREVIEWS

Gut microbiome and orthopaedic health: Bridging the divide between digestion and bone integrity

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Abstract

The gut microbiome, a complex ecosystem of microorganisms in the digestive tract, has emerged as a critical factor in human health, influencing metabolic, immune, and neurological functions. This review explores the connection between the gut microbiome and orthopedic health, examining how gut microbes impact bone density, joint integrity, and skeletal health. It highlights mechanisms linking gut dysbiosis to inflammation in conditions such as rheumatoid arthritis and osteoarthritis, suggesting microbiome modulation as a potential therapeutic strategy. Key findings include the microbiome's role in bone metabolism through

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ARTIGO

Personalized Multimodal Treatment for Adhesive Capsulitis: A Case Series on Regenerative Medicine and Noninvasive Therapies

- Napoliane Costa Santos
- André Vinicius Saueressig Kruel
- Alex Pontes de Macedo
- Fabio Ramos Costa
- Luyddy Pires
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- Palmerindo Antônio Tavares de Mendonça Néto
- Renata Takeyama de Oliveira
- Daiane Agostini
- **José Fábio Lana**

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Personalized Multimodal Treatment for Adhesive Capsulitis: A Case Series on Regenerative Medicine and Noninvasive Therapies

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Abstract

Introduction: Adhesive capsulitis causes chronic shoulder pain and restricted range of motion (ROM). Conventional treatments often offer limited relief, prompting the need for innovative approaches, such as high-intensity pulsed electromagnetic field (PEMF) therapy, shockwave therapy, and orthobiologic injections. Objective: To evaluate the efficacy of a multimodal approach combining shockwave therapy, high-intensity PEMF therapy, orthobiologic injections, and complementary therapies in improving pain and shoulder function in patients with adhesive capsulitis. Methods: This retrospective case series included five patients treated in Indaiatuba, São Paulo, Brazil, between May 2023 and October 2024. Individualized multimodal protocols were performed. Pain and ROM were assessed pre- and post-treatment. Discussion: All patients showed significant improvements in pain and ROM after treatment. High-intensity PEMF therapy, shockwave therapy, and orthobiologics enhanced tissue regeneration, supported by complementary therapies. Personalized protocols optimized outcomes, with synergistic effects observed between treatments. Conclusion: A multimodal, personalized approach effectively reduced pain and improved function in adhesive capsulitis patients. This strategy shows promise, especially for those unresponsive to conventional treatments, warranting further research.

Keywords: Adhesive capsulitis, High intensity pulsed electromagnetic field therapy, Orthobiologics, Regenerative medicine, Shockwave therapy

Introduction

Adhesive capsulitis (AC) or frozen shoulder is a pathology characterized by progressive pain of spontaneous onset in the shoulder associated with stiffness, pain in the shoulder joint and severely limiting mobility. Such restriction is secondary to inflammation of the joint capsule with consequent thickening and adherence of this structure to itself or to the anatomical neck of the humerus [1, 2].
Such comorbidity occurs mainly in females aged 40–60 years, with an incidence of approximately 2%–5% in the general population. This condition not only affects physical activity but can also have profound psychological implications for individuals, leading to frustration and a diminished quality of life due to chronic discomfort [1, 3].

AC is a debilitating condition and understanding the multifaceted nature of AC is crucial. Recent studies indicate that early intervention with physical therapy can improve outcomes and reduce recovery time for some patients. Furthermore, other treatments, such as acupuncture or corticosteroid injections, may provide additional relief for patients who do not respond well to conventional therapies, highlighting the need for a personalized approach in the treatment of this complex condition [4, 5].
While conservative traditional treatment is the first-line approach, many patients experience prolonged recovery and residual functional limitations. The heterogeneity of responses to conservative treatment for adhesive capsulitis, with prolonged recovery in many cases,

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ARTIGO

The Regenerative Marriage Between High-Density Platelet-Rich Plasma and Adipose Tissue

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- Luga Podesta
- **José Fábio Lana**
- George Shapiro
- Rafael Barnabé Domingues
- Andre van Zundert
- Robert W. Alexander

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Pesquisa completa aqui!

International Journal of Molecular Sciences

MDPI

Review

The Regenerative Marriage Between High-Density Platelet-Rich Plasma and Adipose Tissue

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Abstract: The use of autologous biological preparations (ABPs) and their combinations fills the void in healthcare treatment options that exists between surgical procedures, like plastic reconstructive, cosmetic, and orthopedic surgeries; non-surgical musculoskeletal biological procedures; and current pharmaceutical treatments. ABPs, including high-density platelet-rich plasma (HD-PRP), bone marrow aspirate concentrates (BMACs), and adipose tissue preparations, with their unique stromal vascular fractions (SVFs), can play important roles in tissue regeneration and repair processes. They can be easily and safely prepared at the point of care. Healthcare professionals can employ ABPs to mimic the classical wound healing cascade, initiate the angiogenesis cascade, and induce tissue regenerative pathways, aiming to restore the integrity and function of damaged tissues. In this review, we will address combining autologous HD-PRP with adipose tissue, in particular the tissue stromal vascular fraction (t-SVF), as we believe that this biocellular combination demonstrates a synergistic effect, where the HD-PRP constituents enhance the regenerative potential of t-SVF and its adipose-derived mesenchymal stem cells (ADMSCs) and pericytes, leading to improved functional tissue repair, tissue regeneration, and wound healing in variety of clinical applications. We will address some relevant platelet bio-physiological aspects, since these properties contribute to the synergistic effects of combining HD-PRP with t-SVF, promoting overall better outcomes in chronic inflammatory conditions, soft tissue repair, and tissue rejuvenation.

Keywords: high-density platelet-rich plasma; tissue stromal vascular fraction; adipose-derived mesenchymal stem cells; autologous platelet exosomes; tissue repair

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ARTIGO

Cross-talks between osteoporosis and gut microbiome

- SS Jha
- Naveen Jeyaraman
- Madhan Jeyaraman
- Swaminathan Ramasubramanian
- Sathish Muthu
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- **José Fábio Lana**

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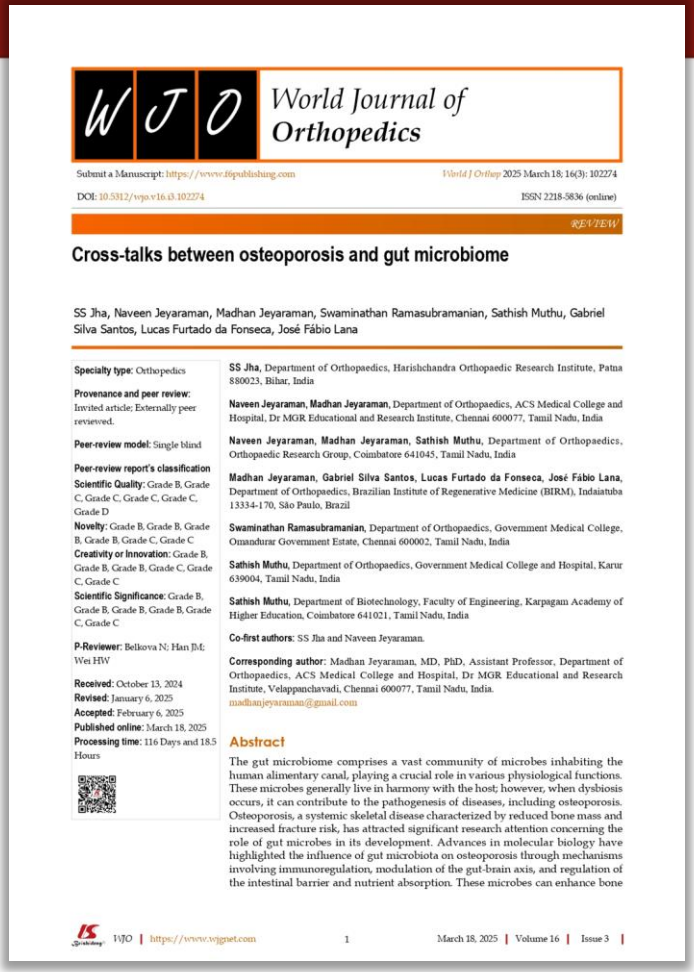

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REVIEW

Cross-talks between osteoporosis and gut microbiome

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Abstract

The gut microbiome comprises a vast community of microbes inhabiting the human alimentary canal, playing a crucial role in various physiological functions. These microbes generally live in harmony with the host; however, when dysbiosis occurs, it can contribute to the pathogenesis of diseases, including osteoporosis. Osteoporosis, a systemic skeletal disease characterized by reduced bone mass and increased fracture risk, has attracted significant research attention concerning the role of gut microbes in its development. Advances in molecular biology have highlighted the influence of gut microbiota on osteoporosis through mechanisms involving immunoregulation, modulation of the gut-brain axis, and regulation of the intestinal barrier and nutrient absorption. These microbes can enhance bone

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ARTIGO

The Role of Injectable Platelet-Rich Fibrin in Orthopedics: Where Do We Stand?

- Fábio Ramos Costa
- Sergio Augusto Lopes de Souza
- Rubens Andrade Martins
- Bruno Ramos Costa
- Luyddy Pires
- Alex Pontes de Macedo
- Napoliane Santos
- Stephany Cares Huber
- Gabriel Silva Santos
- André Kruel
- Márcia Santos
- **José Fábio Lana**

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current issues in molecular biology

MDPI

Review

The Role of Injectable Platelet-Rich Fibrin in Orthopedics: Where Do We Stand?

Fábio Ramos Costa [1,*], Sergio Augusto Lopes de Souza [2], Rubens Andrade Martins [3], Bruno Ramos Costa [4], Luyddy Pires [5,6], Alex Pontes de Macedo [5,6], Napoliane Santos [5,6], Stephany Cares Huber [5,6], Gabriel Silva Santos [5,6,*], André Kruel [8], Márcia Santos [7] and José Fábio Lana [5,6,8,9,10]

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Abstract: Injectable Platelet-Rich Fibrin (i-PRF) has emerged as a promising tool in regenerative medicine, particularly in orthopedics, due to its unique biological properties and ease of preparation. i-PRF is an autologous platelet concentrate derived through a simple, anticoagulant-free centrifugation process, resulting in a liquid matrix enriched with fibrin, leukocytes, and growth factors. These components promote tissue regeneration, angiogenesis, and anti-inflammatory responses, making i-PRF suitable for bone and cartilage repair as well as drug delivery systems. This review discusses the history, biological mechanisms, and clinical applications of i-PRF in orthopedics, highlighting its potential advantages over traditional platelet-rich plasma (PRP). Furthermore, we address the challenges and limitations of i-PRF, including drug stability, release control, and bioactive interactions, underscoring the need for further research to optimize its therapeutic efficacy.

Keywords: platelet-rich fibrin; orthopedics; tissue regeneration; anti-inflammatory therapy; regenerative medicine

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1. Introduction

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate that was first introduced in the field of oral and maxillofacial surgery by Choukroun and colleagues [1]. PRF was initially used in oral and maxillofacial surgical procedures in 2001 by Choukroun et al. due to its simplicity, cost-effectiveness, and ease of handling [2]. This biological product was conceived as a promising alternative to existing bone grafts and platelet-rich plasma at the time [3].

This autologous biomaterial contains a dense fibrin matrix, along with leukocytes and a wide range of healing proteins [4]. Unlike other platelet preparations, such as PRP, i-PRF

ARTIGO

Orthobiologics Revisited: A Concise Perspective On Regenerative Orthopedics

- Fabio Ramos Costa
- Luyddy Pires
- Rubens Andrade Martins
- Marcia Santos
- Gabriel Silva Santos
- João Vitor Lana
- Bruno Ramos Costa
- Napoliane Santos
- Alex Pontes de Macedo
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- **Jose Fabio Lana**

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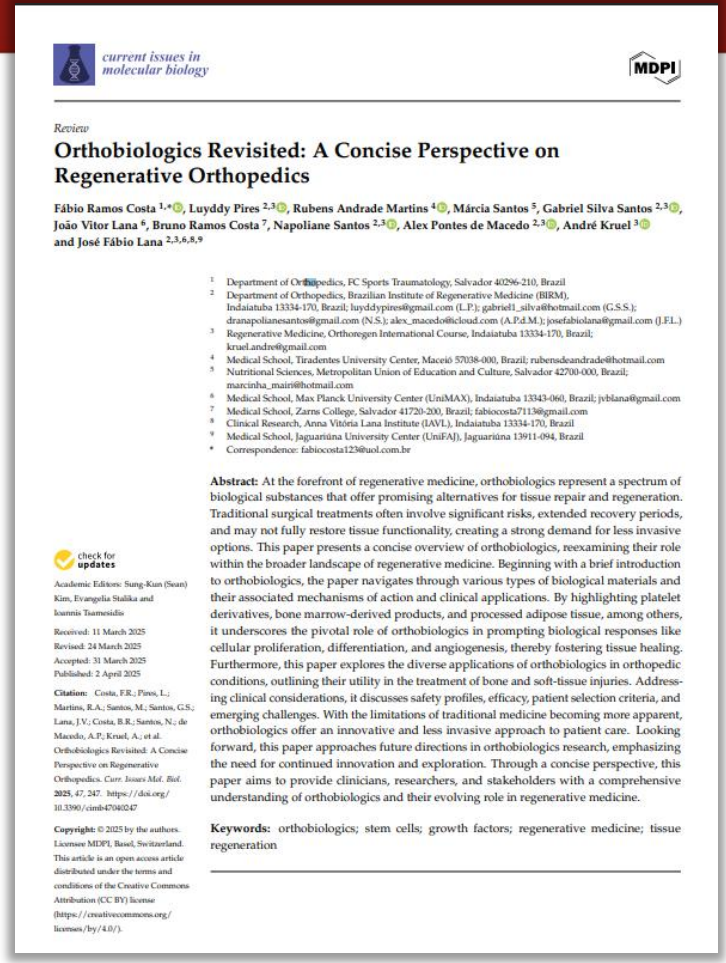

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Review

Orthobiologics Revisited: A Concise Perspective on Regenerative Orthopedics

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Abstract: At the forefront of regenerative medicine, orthobiologics represent a spectrum of biological substances that offer promising alternatives for tissue repair and regeneration. Traditional surgical treatments often involve significant risks, extended recovery periods, and may not fully restore tissue functionality, creating a strong demand for less invasive options. This paper presents a concise overview of orthobiologics, reexamining their role within the broader landscape of regenerative medicine. Beginning with a brief introduction to orthobiologics, the paper navigates through various types of biological materials and their associated mechanisms of action and clinical applications. By highlighting platelet derivatives, bone marrow-derived products, and processed adipose tissue, among others, it underscores the pivotal role of orthobiologics in prompting biological responses like cellular proliferation, differentiation, and angiogenesis, thereby fostering tissue healing. Furthermore, this paper explores the diverse applications of orthobiologics in orthopedic conditions, outlining their utility in the treatment of bone and soft-tissue injuries. Addressing clinical considerations, it discusses safety profiles, efficacy, patient selection criteria, and emerging challenges. With the limitations of traditional medicine becoming more apparent, orthobiologics offer an innovative and less invasive approach to patient care. Looking forward, this paper approaches future directions in orthobiologics research, emphasizing the need for continued innovation and exploration. Through a concise perspective, this paper aims to provide clinicians, researchers, and stakeholders with a comprehensive understanding of orthobiologics and their evolving role in regenerative medicine.

Keywords: orthobiologics; stem cells; growth factors; regenerative medicine; tissue regeneration

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ARTIGO

The Potential of Red Blood Cells in Regenerative Medicine: A Paradigm Shift in Cellular Therapy

- Fábio Ramos Costa
- Joseph Purita
- Ansar Mahmood
- Rubens Martins
- Bruno Costa
- Bruno Lima Rodrigues
- Stephany Cares Huber
- Gabriel Silva Santos
- Luyddy Pires
- Gabriel Azzini
- André Kruel
- **José Fábio Lana**

Publicação: 29 de Maio de 2025
Veículo: MDPI – Cells

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Review

The Potential of Red Blood Cells in Regenerative Medicine: A Paradigm Shift in Cellular Therapy

Fábio Ramos Costa [1,*], Joseph Purita [2], Ansar Mahmood [3], Rubens Martins [4], Bruno Costa [5], Bruno Lima Rodrigues [6,7], Stephany Cares Huber [6,7], Gabriel Silva Santos [6,7,*], Luyddy Pires [6,7], Gabriel Azzini [6,7], André Kruel [6,7] and José Fábio Lana [6,7,8,9,10]

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Abstract: Red blood cells (RBCs) have traditionally been excluded from orthobiologic formulations due to inflammation, oxidative stress, and hemolysis concerns. However, emerging evidence suggests that RBCs may play an active role in regenerative medicine, contributing to immune modulation, vascular support, and oxidative balance. Their interactions with macrophages, involvement in nitric oxide signaling, and release of extracellular vesicles suggest they may influence tissue repair more than previously assumed. Despite these potential benefits, RBC retention in orthobiologic preparations like platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) remains controversial, with most protocols favoring their removal in the absence of robust translational clinical data. This review explores the biological functions of RBCs in regenerative medicine, their potential contributions to PRP and BMAC, and the challenges associated with their inclusion. While concerns about hemolysis and inflammation persist, controlled studies are needed to determine whether selective RBC retention could enhance musculoskeletal healing in some scenarios. Future research should focus on optimizing RBC processing techniques and evaluating their impact on clinical applications. Addressing these gaps will clarify whether RBCs represent an overlooked but valuable component in regenerative therapies or their exclusion remains justified.

Keywords: red blood cells; regenerative medicine; extracellular vesicles; immunomodulation; tissue engineering

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1. Introduction

Regenerative medicine has transformed the treatment of musculoskeletal (MSK) disorders by introducing biologically active therapies that enhance tissue repair and modulate inflammation [1]. Orthobiologic formulations, including platelet-rich plasma (PRP) and

ARTIGO

Integrative review of the gut microbiome's role in pain management for orthopaedic conditions

- Naveen Jeyaraman
- Madhan Jeyaraman
- Priya Dhanpal
- Swaminathan Ramasubramanian
- Arulkumar Nallakumarasamy
- Sathish Muthu
- Gabriel Silva Santos
- Lucas Furtado da Fonseca
- **José Fábio Lana**

Publicação: 20 de Junho de 2025
Veículo: WJEM – World Journal of Experimental Medicine

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World Journal of Experimental Medicine

Integrative review of the gut microbiome's role in pain management for orthopaedic conditions

Naveen Jeyaraman, Madhan Jeyaraman, Priya Dhanpal, Swaminathan Ramasubramanian, Arulkumar Nallakumarasamy, Sathish Muthu, Gabriel Silva Santos, Lucas Furtado da Fonseca, José Fábio Lana

Abstract

The gut microbiome, a complex ecosystem of microorganisms, has a significant role in modulating pain, particularly within orthopaedic conditions. Its impact on immune and neurological functions is underscored by the gut-brain axis, which influences inflammation, pain perception, and systemic immune responses. This integrative review examines current research on how gut dysbiosis is associated with various pain pathways, notably nociceptive and neuroinflammatory mechanisms linked to central sensitization. We highlight advancements in meta-omics technologies, such as metagenomics and metaproteomics, which deepen our understanding of microbiome-host interactions and their implications in pain. Recent studies emphasize that gut-derived short-chain fatty acids and microbial

Livros & Capítulos

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LIVRO

Platelet-Rich Plasma

Regenerative Medicine: Sports Medicine, Orthopedic and Recovery of Musculoskeletal Injuries

- **José Fábio Santos Duarte Lana**
- Maria Helena Andrade Santana
- William Dias Belangero
- Angela Cristina Malheiros Luzo

Publicação: 2014
Editora: Springer

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Minutos em Medicina Regenerativa

- Stephanie Cares Huber
- Lucas Furtado da Fonseca
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- Tomas Mosaner
- **José Fábio Santos Duarte Lana**

Publicação: 2022
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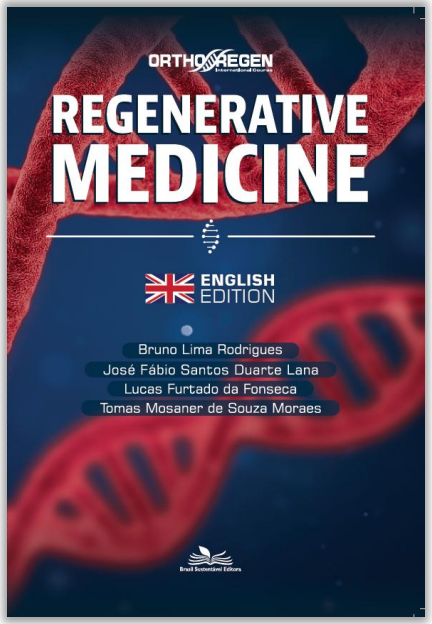
Medicina Regenerativa



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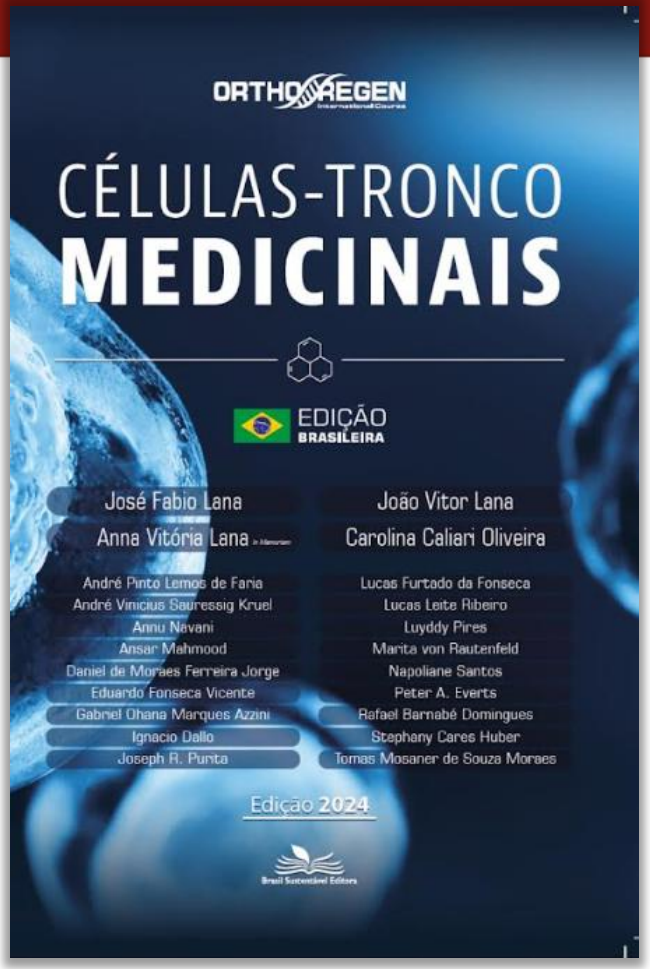

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WoundRegen: Cicatrização Regenerativa

Uma nova Abordagem para o Tratamento de Feridas

Publicação: 2024
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CAPÍTULO

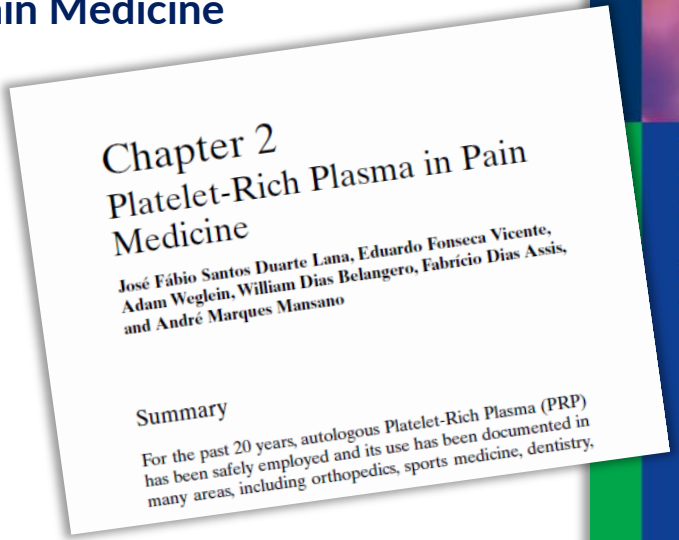
Platelet Rich Plasma in Musculoskeletal Practice

Platelet-Rich Plasma in Pain Medicine

Capítulo 2 / pp 31 – 61

- José Fábio Santos Duarte Lana
- Eduardo Fonseca Vicente
- Adam Weglein
- William Dias Belangero
- Fabricio Dias Assis
- André Marques Mansano

Publicação: 2016
Editora: Springer

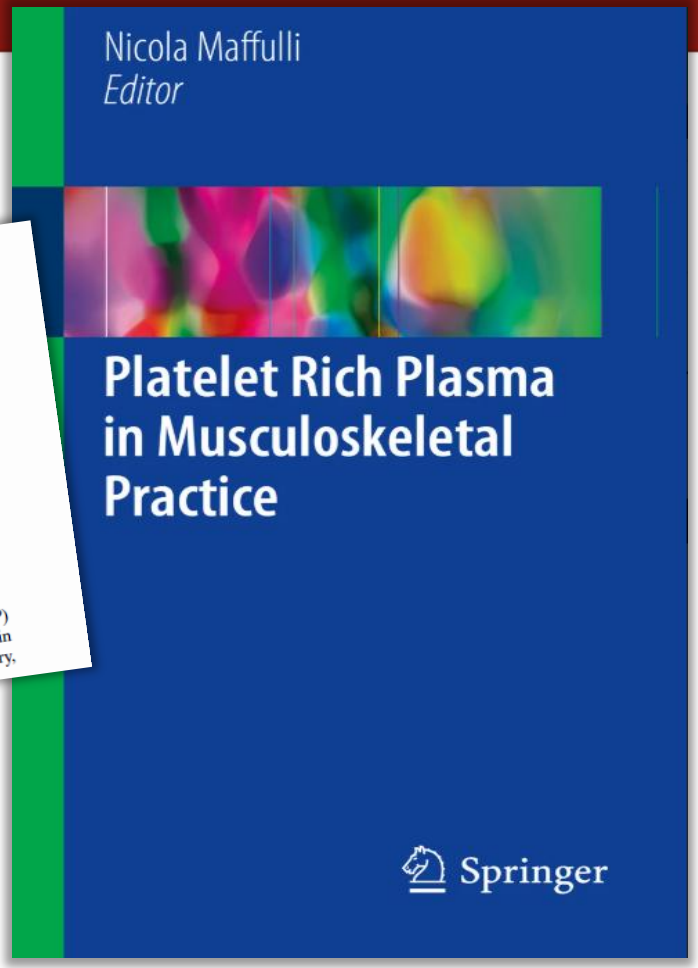


Chapter 2
Platelet-Rich Plasma in Pain Medicine

José Fábio Santos Duarte Lana, Eduardo Fonseca Vicente, Adam Weglein, William Dias Belangero, Fabrício Dias Assis, and André Marques Mansano

Summary

For the past 20 years, autologous Platelet-Rich Plasma (PRP) has been safely employed and its use has been documented in many areas, including orthopedics, sports medicine, dentistry,



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Orthobiologics

Patient Optimization before Regenerative Therapy

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- Gabriel Ohana Marques Azzini
- Lucas Furtado da Fonseca
- Thiago Setti
- Tomas Mosaner
- Lucas Leite Ribeiro
- Marcelo Amaral Coelho
- Anna Vitória Santos Duarte Lana
- **José Fábio Santos Duarte Lana**

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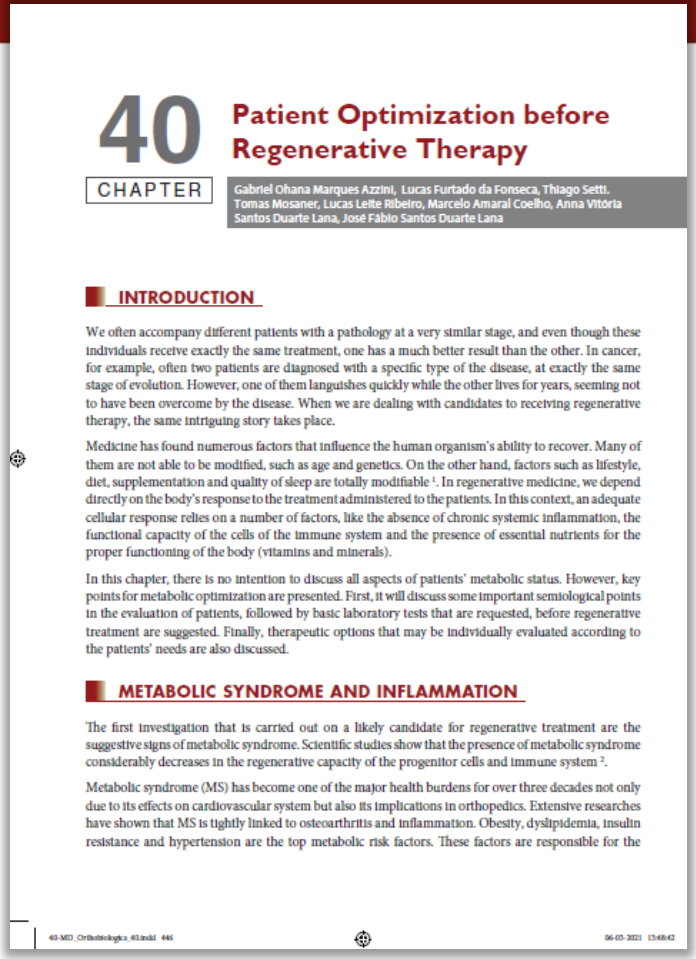

40 CHAPTER

Patient Optimization before Regenerative Therapy

Gabriel Ohana Marques Azzini, Lucas Furtado da Fonseca, Thiago Setti, Tomas Mosaner, Lucas Leite Ribeiro, Marcelo Amaral Coelho, Anna Vitória Santos Duarte Lana, José Fábio Santos Duarte Lana

INTRODUCTION

We often accompany different patients with a pathology at a very similar stage, and even though these individuals receive exactly the same treatment, one has a much better result than the other. In cancer, for example, often two patients are diagnosed with a specific type of the disease, at exactly the same stage of evolution. However, one of them languishes quickly while the other lives for years, seeming not to have been overcome by the disease. When we are dealing with candidates to receiving regenerative therapy, the same intriguing story takes place.

Medicine has found numerous factors that influence the human organism's ability to recover. Many of them are not able to be modified, such as age and genetics. On the other hand, factors such as lifestyle, diet, supplementation and quality of sleep are totally modifiable [1]. In regenerative medicine, we depend directly on the body's response to the treatment administered to the patients. In this context, an adequate cellular response relies on a number of factors, like the absence of chronic systemic inflammation, the functional capacity of the cells of the immune system and the presence of essential nutrients for the proper functioning of the body (vitamins and minerals).

In this chapter, there is no intention to discuss all aspects of patients' metabolic status. However, key points for metabolic optimization are presented. First, it will discuss some important semiological points in the evaluation of patients, followed by basic laboratory tests that are requested, before regenerative treatment are suggested. Finally, therapeutic options that may be individually evaluated according to the patients' needs are also discussed.

METABOLIC SYNDROME AND INFLAMMATION

The first investigation that is carried out on a likely candidate for regenerative treatment are the suggestive signs of metabolic syndrome. Scientific studies show that the presence of metabolic syndrome considerably decreases in the regenerative capacity of the progenitor cells and immune system [2].

Metabolic syndrome (MS) has become one of the major health burdens for over three decades not only due to its effects on cardiovascular system but also its implications in orthopedics. Extensive researches have shown that MS is tightly linked to osteoarthritis and inflammation. Obesity, dyslipidemia, insulin resistance and hypertension are the top metabolic risk factors. These factors are responsible for the

CAPÍTULO

Joint Function Preservation
A Focus on the Osteochondral Unit

“Preparing the Soil”: Optimizing Metabolic Management in Regenerative Medicine Procedures
Capítulo 5 / pp 63 - 73

- Lucas Furtado da Fonseca
- **José Fábio Lana,**
- Silvia Beatriz Coutinho Visoni
- Anna Vitoria Santos Lana
- Eleonora Irlandini
- Gabriel Ohana Marques Azzini

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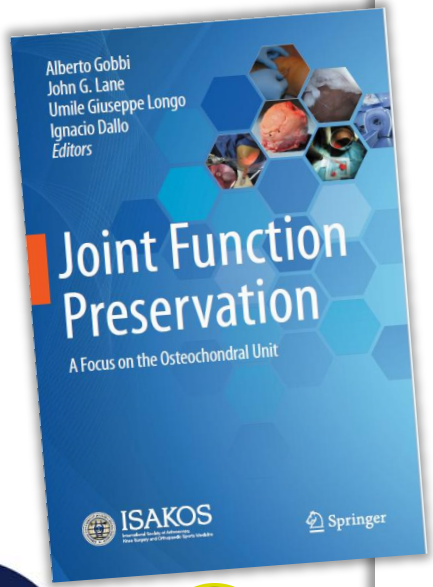

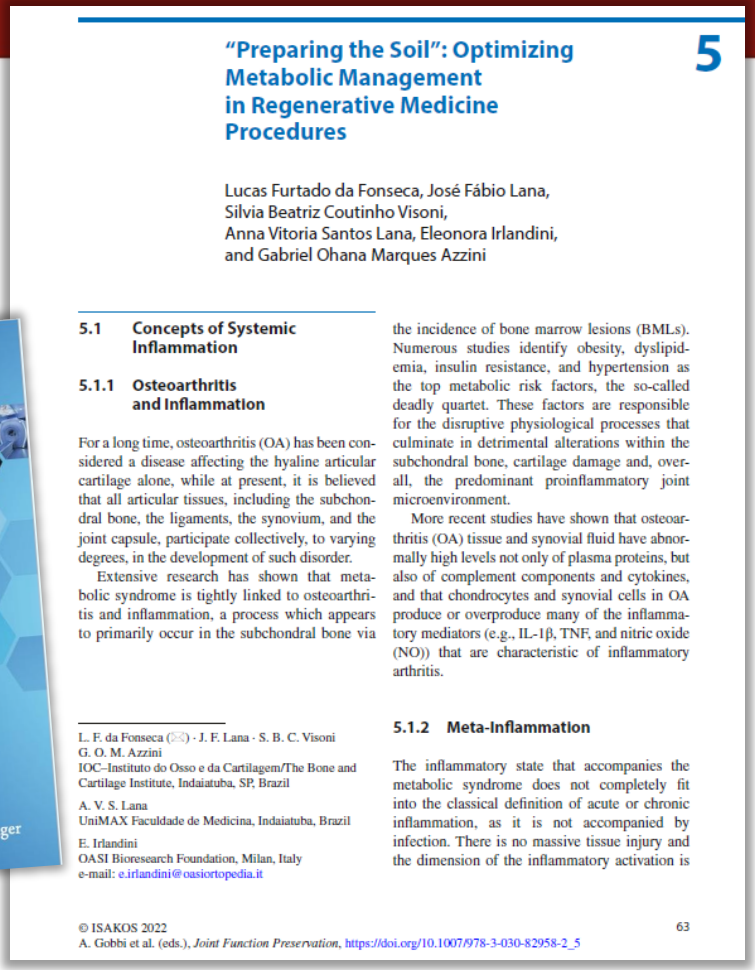

“Preparing the Soil”: Optimizing Metabolic Management in Regenerative Medicine Procedures

5

Lucas Furtado da Fonseca, José Fábio Lana, Silvia Beatriz Coutinho Visoni, Anna Vitoria Santos Lana, Eleonora Irlandini, and Gabriel Ohana Marques Azzini

5.1 Concepts of Systemic Inflammation

5.1.1 Osteoarthritis and Inflammation

For a long time, osteoarthritis (OA) has been considered a disease affecting the hyaline articular cartilage alone, while at present, it is believed that all articular tissues, including the subchondral bone, the ligaments, the synovium, and the joint capsule, participate collectively, to varying degrees, in the development of such disorder.

Extensive research has shown that metabolic syndrome is tightly linked to osteoarthritis and inflammation, a process which appears to primarily occur in the subchondral bone via the incidence of bone marrow lesions (BMLs). Numerous studies identify obesity, dyslipidemia, insulin resistance, and hypertension as the top metabolic risk factors, the so-called deadly quartet. These factors are responsible for the disruptive physiological processes that culminate in detrimental alterations within the subchondral bone, cartilage damage and, overall, the predominant proinflammatory joint microenvironment.

More recent studies have shown that osteoarthritis (OA) tissue and synovial fluid have abnormally high levels not only of plasma proteins, but also of complement components and cytokines, and that chondrocytes and synovial cells in OA produce or overproduce many of the inflammatory mediators (e.g., IL-1β, TNF, and nitric oxide (NO)) that are characteristic of inflammatory arthritis.

5.1.2 Meta-Inflammation

The inflammatory state that accompanies the metabolic syndrome does not completely fit into the classical definition of acute or chronic inflammation, as it is not accompanied by infection. There is no massive tissue injury and the dimension of the inflammatory activation is

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A. Gobbi et al. (eds.), *Joint Function Preservation*, https://doi.org/10.1007/978-3-030-82958-2_5

CAPÍTULO

Muskuloskeletal Injections Manual
Basics, Techniques and Injectable Agents

Bone Marrow Aspirate Concentrates for Knee OA

Capítulo 18 / pp 105 - 115

- Peter A. Everts
- Ignacio Dallo
- **José Fábio Lana,**
- Luga Podesta

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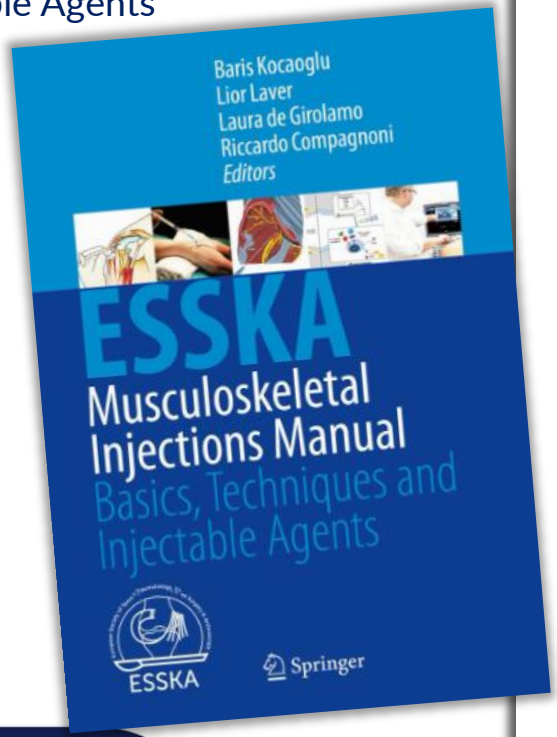

Bone Marrow Aspirate Concentrates for Knee OA **18**

Peter A. Everts, Ignacio Dallo, José Fábio Lana, and Luga Podesta

18.1 Introduction

Orthobiology and regenerative medicine, nonsurgical interventional procedures, involve the use of autologous-prepared biologics to stimulate the body's natural healing processes. These biologics act as a scaffold for tissue repair, immunomodulation, painkilling, and tissue regeneration. The most well-known orthobiological treatment products include platelet-rich plasma (PRP), BMAC, and adipose tissue (AT) preparations. In this chapter we will focus on how to perform a bone marrow aspiration procedure to extract BMA to prepare a BMAC product for injection in patients with knee OA. This procedure can be safely performed by well-trained physicians at POC. The reader should be familiar with their national regulatory requirements to utilize BMAC, which is beyond the scope of this chapter.

18.1.1 Safety and Contraindications

Before performing a BMA procedure, patients should be well informed about the procedure, and it is essential to obtain an informed written consent. Patients need to be informed about potential risks, like infection, hematoma, and anemia [1]. After obtaining an informed consent, any medications, supplements, or activities of daily living that might have an impact in the BMA extraction procedure, bone marrow cell viability, or potential therapeutic effect need to be reviewed and discussed with the patient. It is important that patients avoid specific medications to maintain bone marrow cell viability and post BMAC treatment cellular function in the recipient environment. These medications include nonsteroidal anti-inflammatory drug (NSAIDs), corticosteroid injections, systemic and inhaled steroids, antibiotics (fluoroquinolone), anticoagulants, and statins [2–5]. Contraindications to perform a BMA procedure are severe anemia, active systemic or local infection at the BMA extraction and injection site, and active cancer.

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CAPÍTULO

Muskuloskeletal Injections Manual
Basics, Techniques and Injectable Agents

Alpha-2-Macroglobulin Concentrate as Orthobiologic in Osteoarthritis

Capítulo 21 / pp 133 - 140

- Peter A. Everts
- Luga Podesta
- **José Fábio Lana,**
- Gayan Poovendran
- Gabriel Silva Santos
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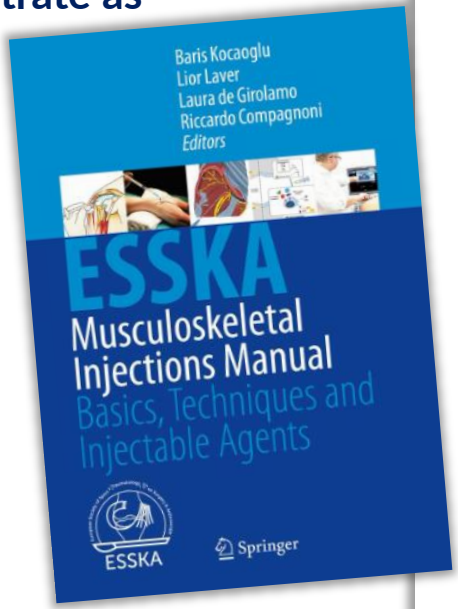

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Alpha-2-Macroglobulin Concentrate as Orthobiologic in Osteoarthritis

Peter A. Everts, Luga Podesta, José Fábio Lana, Gayan Poovendran, Gabriel Silva Santos, and Stephany Cares Huber

21.1 Introduction

Osteoarthritis (OA) is a degenerative and debilitating joint disease and is one of the most prevalent diseases in the United States [1]. OA is characterized by a painful inflammatory disease, causing progressive articular cartilage destruction, limiting patients in their activities. An increase in prevalence and incidence in osteoarthritis can be attributed to many factors, with age and obesity being the most frequent factors [2]. Currently, many orthobiologic treatments options are available to treat various osteoarthritic pathologies (Fig. 21.1). Nonsurgical treatment options are still limited, other than the use of autologous biologics like PRP and bone aspirate marrow concentrate (BMAC), or similar derived products [3]. It has been suggested that A2M, a serum protease inhibitor protein, inhibits the many endogenous and exogenous proteinases presenting in the pathogenesis of OA [4], despite the fact that only few clinical studies report on the application of A2M in OA pathologies [5]. Unfortunately, robust clinical trials are lacking regarding the A2M treatment efficacy and mid- to long-term results.

21.1.1 Safety and Contraindications

A2M proteins are naturally occurring macromolecules and are present in a low concentration in the circulation or in the synovial fluid of joints. In order to be an effective orthobiologic product, it has been suggested to use concentrated A2M as an orthobiologic injectate [6]. Zhu et al. postulated that A2M is an autologous proteinase inhibitor with no autoimmune rejection potential and only one active ingredient, while inhibiting various inflammatory factors and degenerative proteinase [7]. They mentioned no negative effects of A2M injections, or adverse events following the preparation method, which in part is very similar to the preparation of PRP.

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Regenerative Medicine in Sports and Orthopaedics
A New **Approach**

New Treatments for Musculoskeletal Diseases
Capítulo 20 / pp 259 - 269

- Gabriel Ohana Marques Azzini
- Lucas Furtado da Fonseca
- Fabio Ramos Costa
- Silvia Visoni
- Stephany Cares Huber
- **José Fábio Lana**

Publicação: 2025
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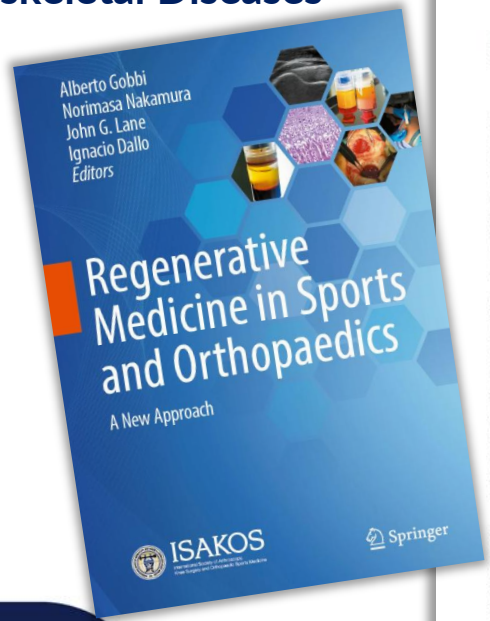

New Treatments for Musculoskeletal Diseases 20

Gabriel Ohana Marques Azzini,
Lucas Furtado da Fonseca, Fabio Ramos Costa,
Dra Silvia Visoni, Dra. Stephany Huber,
and José Fábio Lana

20.1 Principles of Regenerative Medicine

Regenerative medicine is an emerging interdisciplinary field that aims to develop new approaches to repair, regenerate and replace damaged cells, tissues and organs. It has the potential to offer permanent and often curative solutions to the most debilitating ailments by restoring the function of biological tissues and organs that have been impaired. Regenerative medicine in musculoskeletal diseases is of particular significance to patients because the structural changes that underlie degenerative processes in muscle, cartilage, bone and ligament increasingly preclude biologic reversal with conventional therapies that typically aim only to alleviate symptoms by reducing pain and inflammation. Musculoskeletal diseases encompass a broad spectrum of conditions, from spontaneous traumas and autoimmune or molecular aberrations to subtle ageing processes that may follow lifestyle-related behaviours, such as dietary habits or excess body weight, that have a long-term impact on musculoskeletal tissue structure and function. Regenerative medicine offers novel scientific approaches and clinical applications to treat patients with a wide range of debilitating conditions, from traumatic injuries and industrial diseases to spontaneously developed degenerative diseases and age-related tissue wear, including osteoarthritis, autoimmune diseases, osteoporosis and many other diverse musculoskeletal conditions [1–6].

The techniques involved in the field of regenerative medicine are manifold and ever evolving. Cellular therapy exploits the use of cells (often stem cells) to promote the growth and repair of tissue. Embryonic stem cells are pluripotent, meaning these cells possess the ability to differentiate into any type of body tissue. On the other hand, the group of cells known as adult stem cells includes mesenchymal stem cells (MSCs) that are progenitor cells, which can differentiate into multiple cell types, such as bone, cartilage and muscle, depending on the specific microenvironmental cues at the target site of implantation. Tissue engineering consists of the growth of biological tissues on scaffolds (biocompatible supports), seeded with either cells or a combination of cells and bioactive molecules. Although various types of biological tissues can be engineered in vitro, this methodology has been most widely employed to cultivate cartilage, bone and muscle. Cells generated under in vitro conditions

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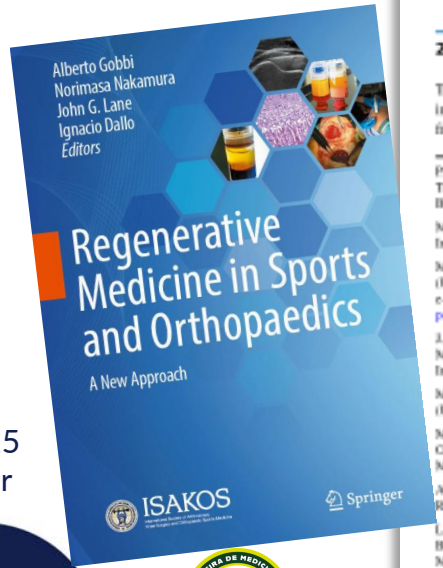
CAPÍTULO

Regenerative Medicine in Sports and Orthopaedics
A New Approach

Essential Considerations in Platelet-Rich Plasma Preparations with Emphasis on Platelet Dosing and Bioformulations: There Is No One-Size-Fits-All Method
Capítulo 22 / pp 291 - 313

- Peter A. Everts
- **José Fábio Lana**
- Melanio Acosta IV
- Luyddy Pires
- Anita van Domselaar
- Alberto Gobbi
- Luga Podesta

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Essential Considerations in Platelet-Rich Plasma Preparations with Emphasis on Platelet Dosing and Bioformulations: There Is No One-Size-Fits-All Method

Peter A. Everts, José Fábio Lana, Melanio Acosta IV, Luyddy Pires, Anita van Domselaar, Alberto Gobbi, and Luga Podesta

22.1 Introduction

There is a pressing need for innovative and less invasive treatment options for patients suffering from a variety of musculoskeletal and spinal disorders [4]. In recent years, autologous biological cellular preparations, freshly prepared at the point of care, have emerged as a promising area of innovative medical healthcare settings. These preparations, including PRP, BMC, and ATC, offer a range of biological materials with potential therapeutic benefits [2]. By harnessing the power of platelets, MSCs, PGFs, leukocytes, signaling cells, cytokines, proteinases, chemokines, and interleukins, orthobiologics can contribute to the advancement of regenerative and orthobiological treatment plans, providing better outcomes for patients suffering from these debilitating conditions [5, 6]. Continued research and collaboration are necessary to further advance the field of orthobiologics and optimize its utilization in musculoskeletal and spinal treatments.

PRP orthobiological applications have shown promising results and are often used to meet the objectives of regenerative medicine therapy initiatives [7]. PRP preparations and treatment protocols have advanced significantly over the last two decades. However, there is currently a lack of consensus regarding standardized protocols for preparing different orthobiological bioformulations [8]. This lack of standardization has led to mixed results in some clinical studies, with some

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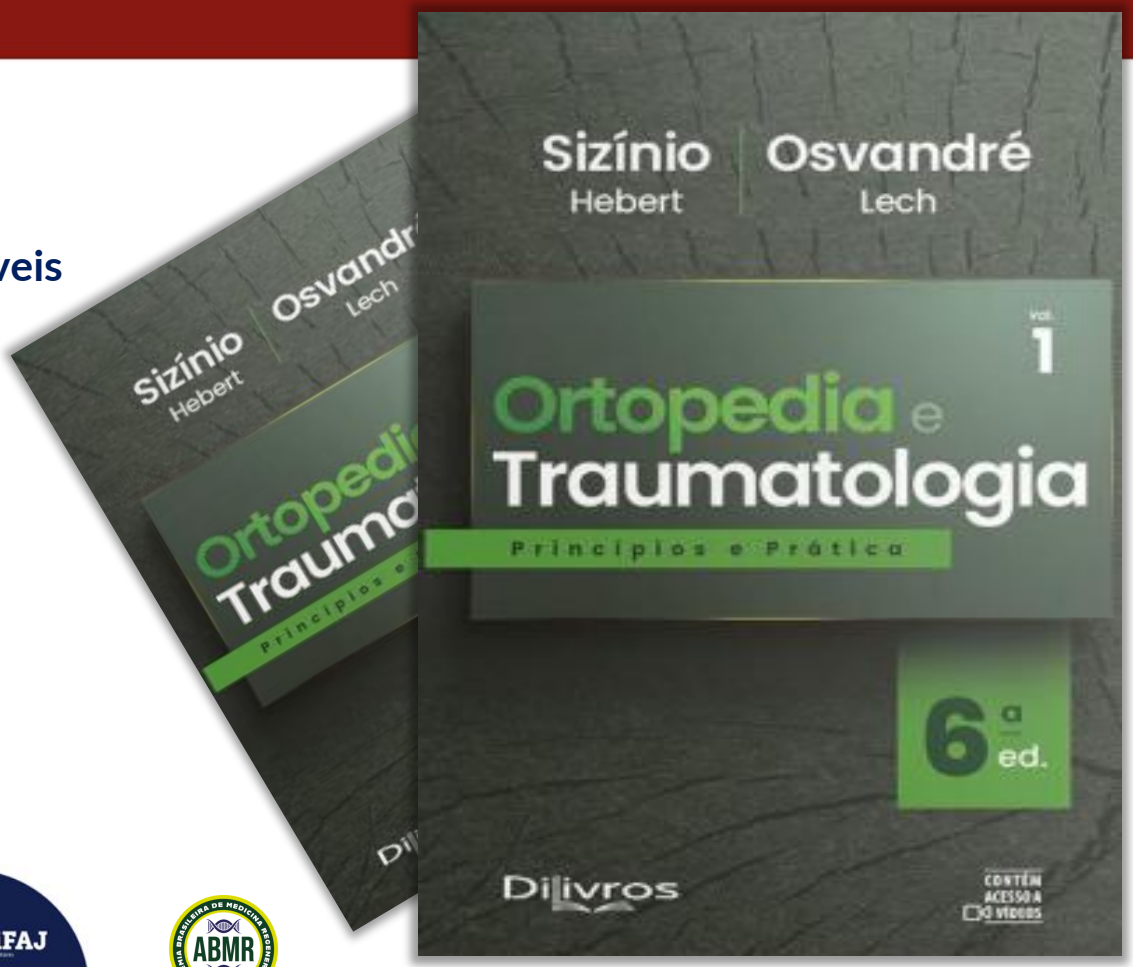

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