Review Article

Platelet Rich Plasma Effects on Diabetic Foot Ulcers - A Review

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Abstract: Utilizing platelet rich plasma, one of the newest autologous cellular therapies, as an adjuvant therapy in a regenerative medicine management, can be very beneficial. Patients with complications like osteoarthritis, spinal disorders and musculoskeletal problems still facing global lacking in the area of tissue repair strategies. Along with this another major complication associated is with diabetic patients - the development of diabetic foot ulcers that predisposes to limb amputation. To advance the healing process and prevent the patients from progressing towards amputations. Besides many other approaches used. Platelet Rich Plasma (PRP) therapy is attaining momentum, which is composed of platelet growth factors that assist the wound healing cascade – inflammation, proliferation and remodeling. It may occur because of provision of vital growth factors necessary for healing. Currently, variety of PRP formulations have been assessed. The article intends to evaluate the PRP effectiveness for managing diabetic ulcers.

Keywords: Platelet rich plasma, Platelet growth factors, Autologous cellular therapy, Diabetic foot ulcer, Osteoarthritis, Inflammation.

INTRODUCTION

Platelet-rich plasma (PRP) which is also known as autologous human plasma is prepared with platelets [1, 2] that are in high concentration exposed to centrifugation. The sample is large amount of patient's own blood. These platelets are overabundant with multiple growth factors as displayed in Table **1** [3]. They are concentrated by the process of centrifugation that aids in the release of supraphysiologic quantities of not only growth factors but cytokines also at injury site to enhance the healing [4, 5]. The typical range of human platelets counts falls somewhere around 150,000 – 350,000/μL and to achieve the healing of bone and soft tissue wounds a concentration of 1,000,000/μL is required. This high amount increases the growth factors up to 3 to 5 folds [6]. Variety of PRP formulations are available together with Leukocyte-rich PRP (LR-PRP) – high neutrophil concentration beyond baseline and Leukocyte-poor PRP (LP-PRP) - leukocyte (neutrophil) concentration under baseline [7]. Diabetes mellitus is very common and most prevalent disease globally. The International Diabetes Federation data indicated that, 1 out of 11 among 415 million adults have been suffering from diabetes. Out of them almost 15% faces the complications of diabetic foot ulcers (DFU) [2] that further lead to severe consequences related to lower limb amputation in more than 88% cases mediated by necrosis [8], gangrene and osteomyelitis [9-11]. These ulcers are pool for variety of infections so early treatment is necessary [12]. DFU being the principal source of limb amputations, these ulcers are commonly developed by neuropathy, foot deformities, peripheral arterial disease and any overlooked minor trauma. The process of ulcer healing is delayed in diabetes that makes these foot ulcers chronic [13] which are often hindered at the initial step of healing cascade – inflammation. Additionally impairment in granulation tissue formation is also observed [14, 15]. Hence, DFU is a severe diabetes mellitus-related problem [16] persuaded by uncontrolled glycemic level, leading to vascular complications and peripheral neuropathy. Due to the functioning biomolecules in PRP that promote analgesia, immunomodulation, angiogenesis, and cell proliferation for managing both acute and chronic wounds, it may be favorable for healing progressions [17, 18].

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Table 1. Growth Factors in PRP

Growth Factors
Platelet-Derived Growth Factor [19]
Transforming Growth Factor -β [20]
Vascular Endothelial Growth Factor [21]
Epidermal growth factor [20]
Hepatocyte Growth Factor [22]
Fibroblast Growth Factor [23, 24]
Insulin-Like Growth Factor 1 [25, 26]

METHODOLOGY

English language articles only are included. Literature was explored in Google Scholar and PubMed by using standard keywords as mentioned in Table **2**. The articles are included with no exclusion criteria from the years 2000 -2022. Observational studies, randomized controlled trials, and systematic reviews made up the majority of the recently evaluated literature, which is current as of September 2022.

Table 2. Article Selection Methodology.

Keywords	**Results**	**Results after utilizing inclusion criteria**	**MeSH Keywords applied**	**Results after using inclusion criteria**
Diabetic foot ulcer	17,200	13,600	Diabetic foot/complications	493
Diabetes foot care	37,500	14,700	Diabetic foot/therapy	1,534
Management of diabetic foot ulcer	17,300	11,400	Platelet rich plasma for diabetic foot ulcer	121

RESULTS

By exploring data on Google scholar and PubMed 121 articles were reviewed after applying inclusion criteria from which 100 are included in our review.

DISCUSSION

Wound healing is complex which involves numerous cell populations, soluble mediators and extracellular matrix i.e. growth factors and cytokines [27-29]. A number of abnormalities have been reported in diabetics that could modify wound healing biology. Diabetic foot ulceration can be led with interaction of the buildup of enhanced glycation end-products with inflammation [14]. Also, the wound healing cascade can be influenced by injurious hyperglycemia effect on neutrophil activities. Elastases and metalloproteinases, two enzymes generated by neutrophils, are accountable for the breakdown of the peptide growth factors and extracellular matrix required in wound cure [30-33]. Moreover, there is unusual expression of growth factors in DFU [14, 34, 35]. Additionally, skin insensitivity evolving from autonomic modifications which damage the sweat glands function, leads to more nodule formation. There is additional influence on the mechanics of weight bearing and gait due to damaged sensorimotor neurons that inexplicably lead to decreased or changed sensation [16].

Precise synthetic growth factors to be applied topically for treatment of DFU have been suggested due to the pathologic anomalies observed in diabetics. These synthetic growth factors comprise recombinant human platelet derived growth factor (rh-PDGF-BB), recombinant human basic fibroblastic growth factor (rh-bFGF) and recombinant human vascular endothelial growth factor (rh-VEGF-A) [12, 36, 37,38]. FDA approved the topical rhPDGF-BB application, more thorough research is required to determine how recombinant PDGF works to treat DFU [39,40]. However, addressing the biological issues with DFUs by employing just one growth factor might not be sufficient [14].

PRP Application is another approach suggested to manage DFUs which is established on the abundance and complex discharge of such cells that involve above 300 proteins [41]. PRP comprises protease inhibitors, growth factors, cytokines and antimicrobial apart from coagulation and associated proteins. PRP can also recruit macrophages owing to its chemotaxis characteristics and acts as an anti-infective too [42, 43]. Utilizing PRP to deal with DFU can be beneficial methodology established on the pathophysiology of diabetic wound healing, but good evidence is lacking [44]. There are suggestions to use PRP on DFU which stay unhealed following standard therapy [45]. Nevertheless, the expenses of PRP treatment for DFUs are seemingly higher than the standard therapy [46]. Due to this cause, application of this methodology could be problematic for DFU treatment and should be built on its cost-effectiveness [14].

Updates on the Management of Diabetic Foot Ulcer

The conventional procedures in DFU management are: surgical debridement [47-50], dressings facilitating a moist wound setting and control of exudation [51], wound off-loading [52,

53], vascular evaluation [54], and infection [55, 56] and glycemic control [57-59]. A multidisciplinary diabetic foot wound facility is the best place to handle these treatments [60, 61]. The recommendations for existing approaches and the effectiveness of adjuvant agents include these types: nonsurgical debridement agents [62], dressings and topical agents, oxygen therapies [63], negative pressure wound therapy [64], acellular bioproducts [65], human growth factors [40, 66-71], energy-based treatments, and systemic therapies. Though the majority of the evidence come from small-scale, randomized controlled studies with higher potential of bias, several of these medications have proved helpful to increase wound healing rates. [72-75].

Composition and Formulation of PRP

There is no concordance in general on the finest possible PRP formulation with regard to blood components concentration and there are several PRP procedures available in the market. Variations are existing in protocols of PRP collection and formulation properties dependent on the market, offering PRP procedures in distinctive characteristics [4, 7, 76, 77]. In commercial markets, there are often differences in their platelet capture efficacy, isolation technique, centrifugation velocity, and the kind of collection tube method. In general, there is collection of whole blood [78, 79] for PRP production. Anticoagulants are included for prevention of premature secretion of the alpha granules [80], preceding to centrifugation, which splits RBCs from platelet-poor plasma (PPP) and the "buffy coat," which encompasses the concentrated platelets and leukocytes (Fig. **1**).

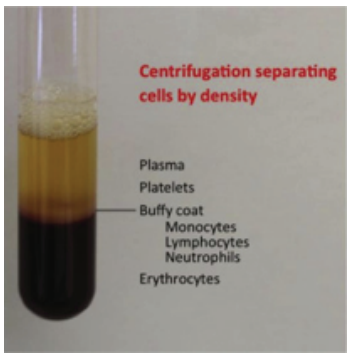

Fig. (1). Whole blood Separation by Centrifugation.

The patient-specific aspects, inclusive of drugs taken, and commercial system formulation techniques both affect the precise PRP makeup. This inconsistency in the composition of PRP formulation produces difficulties to interpret the literature about the PRP's clinical efficacy [7, 81]. When combined with autologous platelet-rich plasma, leukocyte- and platelet-rich fibrin (L-PRF) has proven to be an efficient adjuvant therapy for managing DFUs (PRP). PRP effectiveness results can be contradictory because of lacking of uniformity in the PRP formulation procedure and the scarcity of well-conducted RCTs [82].

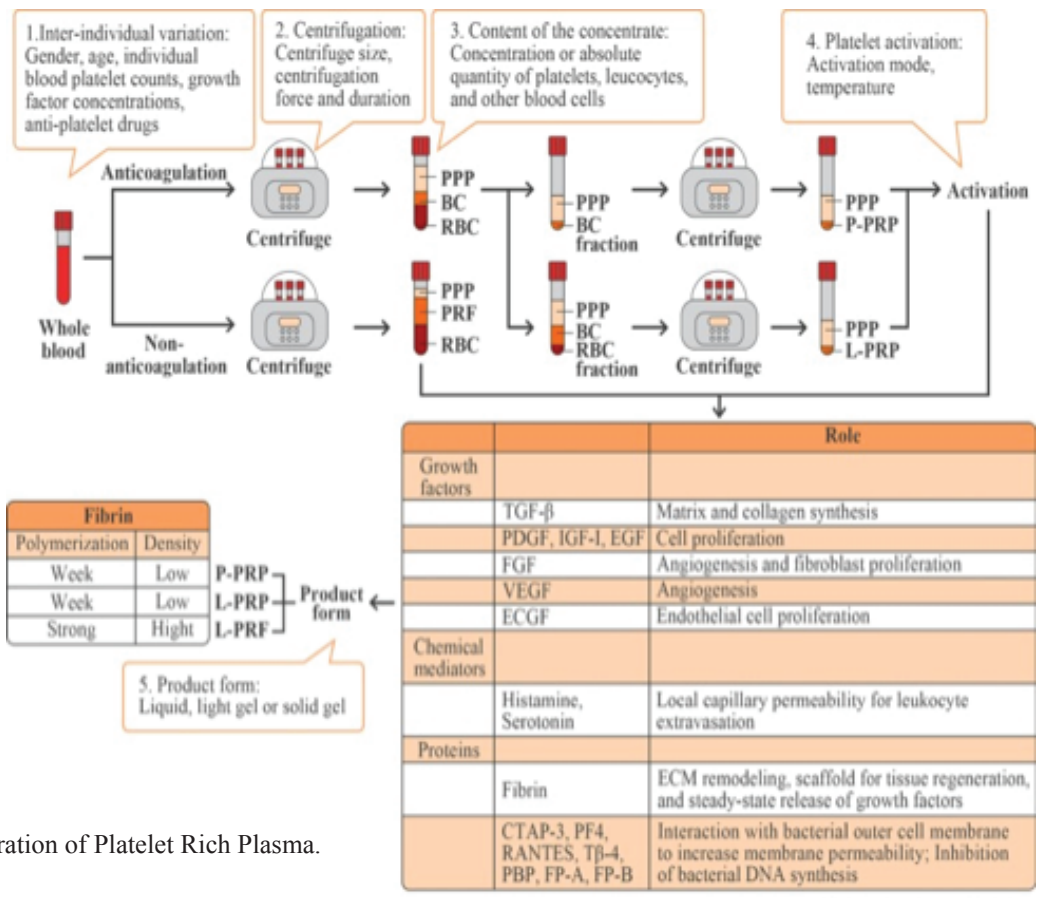

Fig. (2). Preparation of Platelet Rich Plasma.

Pure PRP (P-PRP) and leukocyte- and platelet-rich plasma (L-PRP), are the main classifications of PRP, which are separated by fibrin architecture and cell components [83-88]. P-PRP is created after activation, deprived of leukocytes and with a low-density fibrin network whereas, numerous leukocytes are there in L-PRP. The typical process consist of two sequential centrifugation phases (Fig. **2**). In first phase, the blood components are separated into 3 tiers namely red blood cell layer, buffy coat layer and poor platelet plasma. In the subsequent phase, PRP, concentrated platelets are extracted from a little amount of plasma. P-PRP and L-PRP may be distinguished from one another only when the buffy coat has been assembled completely or partially for second centrifugation (Fig. **2**). When the buffy coat is not fully or just partially collected, P-PRP is created. PRP can then be activated by various substances such as calcium chloride, bovine thrombin, collagen, or mechanical stress [82]. There is only one product found in P-PRF, and that is platelet-rich fibrin matrix (PRFM). One tube is for blood collection, and the other tube is for PRFM clotting. Due to the high cost and complexity of this methodology, it is not commonly employed. The L-PRF formulations include a 3D-designed fibrin matrix as well as a lot of leukocytes [89]. Hence, unlike P-PRP/L-PRP, PRF dissolves very slowly after administration. Moreover, the formulation of L-PRF is entirely natural as it has one-step centrifugation with no use of anticoagulants or activators; this is a fundamental difference amid all other types of PRP formulations. So, this method is very simple, rapid, and cost effective to prepare the PRP. Consequently, L-PRF is regarded as second-generation of platelet concentrate, to be commonly employed in clinical practice [82, 90]. In addition to growth factors, activated PRP platelets release significant amounts of substances that support primary homeostasis, such as fibrinogen, fibronectin, serotonin, factor V,VI and VIII. These cause platelet aggregates to form (clots), which stabilise the platelets by creating cross-linked fibrin and sticky glycoproteins [91].

The capability of PRP in improving DFU healing has been assessed in many RCTs. It has been observed that the therapeutic effects of PRP are stronger and more consistent in DFU than in other injuries. According to reports, a statistically significant difference between conventional care and the percentage and pace of DFU recovery was found in 10 out of 12 controlled trials. Furthermore, after PRP usage, uncontrolled trials also exhibited greater healing rates that range from 0.385 to 0.867 cm2/week. Such results reveal the distinct benefits of PRP to treat DFUs. Some recent studies suggest that PRP may contain anti-inflammatory activities so it may show further beneficial effects on infection prevention [82]. Yet, more vigorous clinical trials are needed to establish such activities [92, 93] before PRP is tried for treating chronic wound infections and osteomyelitis. Few of the uncontrolled trials reported decrease in pain in DFU patients after PRP use, as observed by a decline in intake of then analgesics. Thus, administration of platelet concentrates for DFU treatment, particularly for refractory and chronic wounds, exhibits favorable outcomes, together with a reduction in inflammation or infection, accelerated DFU healing, and decreased use of analgesics [82, 87, 94, 95].

As per 2017 data, there had been no conduction of substantial and evidence-based study for PRP [48]. The existent trials validating positive outcomes of PRP [38] can be methodologically debatable or be considered as not showing considerable improvement in DFU healing in comparison to control group or cases managed by standard processes [44, 96]. Nevertheless, considerable improvement in DFU healing with PRP usage combined with other therapies had been reported [12, 96].

55 individuals total were enrolled in the trial, of whom 29 cases were in the study group and 26 cases were in the control group. The mean wound score in the study group significantly improved following PRP therapy (p 0.0001). In all cases of the study group, the wound completely healed in 36.7 days on average and 3.3 days on average, compared to 60.6 days on average for the control group (p 0.0001). Due to the use of PRP, undesirable effects were not noticed in this investigation [97].

A randomised control trial for DFU included 24 cases, with a mean age of 55.2 6.4 years, split into 2 groups. Comparatively to group II cases, where none displayed complete healing, three (25%) of the cases in group I achieved overall recovery. The DFU's longitudinal and horizontal shrinkage percentages were significantly larger in group I than in group II. When compared to group II, group I required significantly less time to reach maximum recovery. According to reports, PRP gel dressing for chronic DFU significantly reduced the size of the ulcer compared to ordinary saline dressing. Additionally, PRP dressing offered the fastest healing time feasible with the smallest size of wound [84].

In a different study, 10 DFU RCTs with a total of 456 cases were examined. In the meta-analysis, which compared the PRP group to controls, it was found that there was a higher rate of complete ulcer recovery 1.32 pooled relative risk, a shorter recovery time and a decrease in the incidence of adverse events. The results were not significantly changed by the application of the trim-and-fill technique, despite the fact that different data were identified for publication bias. According to the reports, autologous PRP may speed up the healing of all ulcers, reduce recovery time, and increase adverse effects [85].

The management of DFU with and without PRP was examined using the data from 20 RCTs and 5 observational studies. In lower-extremity diabetic ulcers, it was analyzed that the PRP use significantly increased total wound closure,

decreased time to complete wound recovery, and decreased wound region and depth (low SOE). Significantly detrimental alterations were observed in the instances of wound infection, amputation, wound relapse, or hospitalization [98].

PRP Mechanisms in DFU

PRP's effects on wound healing may primarily result from the release of various bioactive molecules along with growth factors, chemokines, and cytokines gathered in platelets [40]. PRP comprises of several significant proteins apart from growth factors, like fibrin which may affect remodeling of ECM. Also, PRP holds a number of antibacterial proteins upon activation (Fig. **2**). PRP can be deemed as adjunct therapy for infections, in cases of multidrug resistant bacteria particularly [82,99,100].

CONCLUSION

There has been increase in the utilization of autologous PRP for DFU management. However, the extensive use of PRP is hindered by its complex preparation process and high cost of PRP. It is expected in the near future that modest and low-cost methods, like L-PRF, may be broadly utilized. The potential benefits of PRP must be wisely considered. The evidence-based application of autologous PRP is continuously emerging with the ongoing clinical trials to prove its efficacy. Though, data related to its complete therapeutic effectiveness is still lacking. The uniform technique of PRP formulation and well-planned RCTs with huge sample sizes may reduce the disparities on related outcomes and benefit to reexamine its clinical efficacy. It is expected that platelet concentrations that develop PRP, may turn out to be clinically efficient, cost-effective and easy adjunct for the treatment of DFUs.

CONFLICT OF INTEREST

Declared none.

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