The Effect of Diet on Platelet Rich Plasma (PRP) Based Treatments

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Abstract

Background: Platelet-rich plasma (PRP) is prepared from autologous blood samples for therapeutic use across many specialities including orthopaedics and regenerative medicine. The increasing use of PRP is underpinned by an intrinsic capacity to release multiple, platelet-derived growth factors at super-physiological concentrations promoting tissue repair.

Objectives: Evidence and guidance towards the most efficacious use of PRP is scarce across several domains including: patient pre-optimisation (such as diet or exercise); The purpose of this review was to summarise current knowledge and highlight areas that require further investigation.

Study Design & Methods: Two literature searches were conducted on Wednesday 26th May 2021 on Medline and using the keywords: ["PRP" OR "Platelet-rich Plasma" OR "Platelet Rich Plasma"] AND Diet; ["PRP" OR "Platelet-rich Plasma" OR "Platelet Rich Plasma"] AND "Platelet Function". All relevant papers were reviewed in full and results, where available, are summarised.

Results: Significant diet-induced changes in platelet aggregation were found in 5 studies identifying dark chocolate, energy drinks, dietary nitrate, aged garlic extract, and diets high in saturated fats or flavonoids as potential effectors. Of these, all except energy drinks decreased platelet aggregation. Other agents including ketorolac, propacetamol and magnesium were all reported to reduce platelet activation whilst cyclosporin A had the opposite effect. Limited evidence suggests a short-term increase in platelet aggregation and activation following moderate to high intensity exercise, with a subsequent reduction in the longer-term.

Conclusions: Patients should be advised to reduce intake of those diets reported to decrease platelet activation. Although energy drinks were found to increase platelet aggregation the causative ingredient has not been identified and other factors (calorie content) should be considered. Further studies are required to identify the active agent(s). We propose that ketorolac, propacetamol and magnesium be added to drugs, use of which are advised against prior to PRP collection. The potential for cyclosporin A to be used as an agent to increase platelet activity should be examined in clinical trials where safety outcomes are thoroughly assessed.

Evidence detailing the effect of exercise on platelet activity and function is inconclusive and further studies, including measurement of platelet count, aggregation and release of growth factors, are recommended.

Keywords: cyclosporin • ketorolac • propacetamol

Introduction

Platelet-Rich Plasma (PRP) is a form of therapy prepared from autologous blood samples. It has been described previously as a portion of the plasma fraction of autologous blood with a platelet concentration above the baseline (before centrifugation) or specifically with a platelet count of 1,000,000/µl in 5ml volume of plasma [1].

It's applications so far as a form of therapy have been across a wide range of specialities including cardiothoracic surgery, cosmetic, dermatology, musculoskeletal (MSK), neurology, oral maxillofacial surgery, ophthalmology, and plastic surgery [2]. It was discovered in 1914 by Dimond et al. but its applications clinically have come much more recently, being in wider use since the 1970's. In addition, there is not much in the literature on patient factors or pre-treatment regimes which may affect the quality or composition of the final PRP preparation.

It's use in regenerative medicine is based on the release of multiple growth factors from platelets harnessed in PRP in super natural concentrations to promote tissue repair . Growth factors released include platelet derived growth factors -AA, -AB, -BB (PDGF-AA, PDGF-AB, PDGF-BB), Transforming Rowth Factor Beta 1 (TGFB1), Vascular Endothelial Growth Fac- tor (VEGF), Epidermal Growth Factor (EGF), and Insulin-like Growth Factor (IGF) [3]. The presence of multiple growth factors, chemokines and other factors appears to be important as TGFB1 or PDGF alone does not have the same mitogenic effect as PRP. Both in vitro and animal studies have shown PRP to influence migration, proliferation and differentiation for a number of cell types. Animal studies have shown both promotion of bone regeneration and increases in strength of transected and lesioned tendons [4]. Many studies have examined the effect of PRP as adjunctive treatment in comparison to primary treatment without PRP. Nazaroff et. al. found in their systematic review of clinical trials that 61% found PRP to be favourable to control treatment.

Despite the large number of studies studying the effects of PRP, heterogeneity with between studies in preparation and reporting means evidence to support its use is inconclusive so far. This variation is reflected in the "high" risk of bias shown in studies assessed using the Cochrane risk of bias tool [2]. So far evidence is scarce in the following domains: patient pre-optimisation; optimal platelet counts for therapeutic effect; standardised quality checks-whether measures of platelet counts, growth factors or platelet aggregation are more clinically useful.

The purpose of this review was to summarise the current knowledge on these factors and highlight areas where there remains a need for robust pilot and clinical trials. Two literature searches were conducted on Wednesday 26th May 2021 on both Medline and using the keywords:

1. ["PRP" OR "Platelet-rich Plasma" OR "Platelet Rich Plasma"] AND Diet
2. ["PRP" OR "Platelet-rich Plasma" OR "Platelet Rich Plasma"] AND "Platelet Function" AND "Randomised Control Trial" OR "Trial" OR "Clinical Trial"

All relevant papers were reviewed in full and results where available are summarised.

Diet and Platelet Function

The overwhelming majority of papers examining patient factors and their effect on platelet function look at diet and its influence. Many of the dietary supplements and foods studied were theorised to reduce platelet aggregation and function in order to be beneficial in reducing cardiovascular event risk. For the purpose of PRP injection, it is likely beneficial to have maximal platelet function in the PRP collected in order to have a maximal amount of growth factors released. We therefore need to examine these studies from the opposite perspective. 29 papers were identified in the literature search which examine dietary effects on platelet function. 6 were excluded from this summary – 3 animal studies, 2 with no relevant outcomes, 1 duplicate. A summary of each study examined can be found in table 1 below.

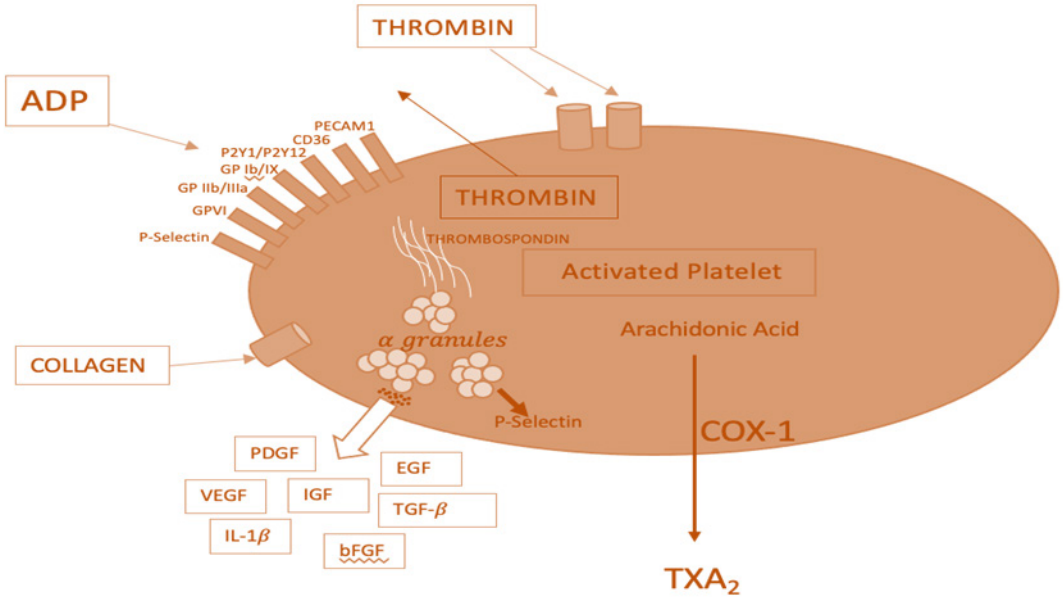

Figure 1. Adapted from Barale, Russo 2020. Diagram of biochemical factors involved in the coagulation cascade following platelet activation. AA (arachidonic acid); COX (cyclooxygenase); TXA2 (thromboxane A2); PDGF (platelet-derived growth factor); TGF-β (transforming growth factor β); EGF (endothelial growth factor); bFGF (fibroblast growth factor); VEGF (vascular endothelial growth factor); IGF (insulin-like growth factor); IL-1β (interleukin-1β).

Table 1. Summary of all relevant studies found on diet and PRP.

Study	Study type; Participants; Treatment Arms	Results
Hendra et. al. 1990	RCT; 8 NIDDM patients; 5 MaxEPA capsules (each containing 1 g fish oil) twice a day, 5 olive oil capsules.	Agonist-induced platelet aggregation in either whole blood or platelet-rich plasma was unaffected by either MaxEPA or olive oil.
Hansen et. al 1993	Crossover study; 34 healthy participants; 25ml cod liver oil, placebo.	After cod liver oil intake, platelet sensitivity to collagen in PRP decreased in men only ($P < 0.01$), and the response was significantly different from that in women ($P < 0.05$)
Freese, Mutanen 1995	Non-randomised clinical trial; 12 healthy females; High-fat meals.	Platelet aggregation induced by collagen (0.6, 1 and 2.5 micrograms/ml) decreased during the 5-h period after the meals ($P = 0.000$). ADP-induced aggregation did not change during the follow-up period after any meal ($P = 0.105$-0.483).
Janssen et. al. 1996	Crossover study; 18 healthy participants; 15g of raw ginger root; 40 g of cooked stem ginger, placebo.	Mean decrease in platelet thromboxane production relative to placebo was 1 +/- 9% for ginger root, and -1 +/- 8% for stem ginger, with no effect of treatment order ($P = 0.984$).
Nelson et. al. 1997	Crossover study; 12 healthy participants; 1.7 g/d of AA, basal diet which contained 210 mg of AA.	No statistically significant changes in either the aggregation values or the platelet counts when the results from the two diets are compared
Nelson, Schmidt et. al. 1997	Longitudinal study; 12 healthy participants; High DHA diet, Low DHA diet.	No statistically significant changes in either the aggregation values or the platelet counts when the results from the two diets are compared.
Benito et. al. 2001	RCT; 17 healthy females; conjugated linoleic acid (CLA), sunflower oil	No statistically significant change in either the aggregation values or the platelet counts when the results from intervention and control groups were compared.
Innes et. al. 2003	RCT; 30 healthy participants; 100g dark chocolate, 100g milk chocolate, 100g white chocolate	Dark chocolate inhibited platelet aggregation and reduced the rate of aggregation induced by collagen but not ADP. PRP aggregation fell from median values of 73% before chocolate to 64% after ($p=0.025$) and 53% to 4% (93% drop) ($p=0.028$) in 1µg/ml and 0.5µg/ml collagen-induced aggregation respectively after chocolate consumtion. Milk chocolate induced a small reduction in aggregation induced by 0.5µg/ml collagen but this failed to reach statistical significance. White chocolate had no significant effect on the platelet function tests.
Worthley et. al. 2010	RCT; 50 healthy participants; 250ml sugar free energy drink, 250ml carbonated water	Platelet aggregation increased after energy drink consumption, compared with the control group. The increases are seen at both low and high-dose adenosine diphosphate induced aggregation. This was statistically significant for the low dose ADP induction $P <0.003$
Miller et. al. 2014	Longitudinal study; 64 healthy participants; flavonoid rich food exposure	Of 75 specimens drawn after flavonoid-rich food exposures, 24 (32.0%) had aberrant results, compared to 4 of 47 specimens (85%) without such exposures ($P = 00035$). The distribution of exposures was significantly different between the aberrant and non-aberrant specimens ($P < 0.0001$). Of 28 specimens with aberrant results, 24 (85.7%) were drawn after flavonoid-rich food intake within 18 h, compared to 51/94 (54.0%) with consistent results ($P = 0.0035$). Exposure within 1–6 h with or without earlier exposure characterized 19/94 specimens (20.2%) with non-aberrant results and 15/28 (53.6%) with aberrant results ($P = 0.0004$).
Velmurugan et. al. 2013	Crossover study; 24 healthy participants; 250ml beetroot juice; potassium nitrate capsules; placebo	Dietary nitrate administration, in the form of beetroot juice, caused a significant rise in plasma nitrite and nitrate. The concentration–response curves to both ADP and collagen, but not epinephrine, were significantly suppressed following dietary nitrate treatment in males but not females. The placebo had no effect on platelet responses to any aggregating stimuli in either sex.

Kusumoto et. al. 2007	RCT; 28 healthy males; 200mg arachidonate-enriched triacylglycerol capsules; 200 mg/ capsule olive oil	No significant differences were observed in aggregation response between the two groups.
Rahman, Billington 2000	Longitudinal study; 23 healthy participants; 5ml aged garlic extract/day for 13 weeks	The extent of platelet aggregation in response to ADP was reduced after dietary supplementation with 5 mL of AGE/d for 13 wk. This was most dramatic at low concentrations of ADP (P = 0.05; 0.5, 1 and 2 μmol/L). At ADP concentrations ≥ 4 μmol/L, total percentage aggregation was maximal at 70 – 80% and was not significantly affected by ingestion of AGE. The rate of ADP-induced platelet aggregation was similarly reduced after dietary supplementation with AGE (Fig. 1B). This was significant at all concentrations of ADP up to 10 μmol/L.
Imano et. al. 1998	Cross-sectional study; 306 japanese males aged 50-70; dietary intake of fish, seafood and soy bean foods were inquired using one-week dietary records	Serum n3-polyunsaturated fatty acid, and gamma-GTP, as an index of alcohol intake, reduce platelet aggregation while age, white blood cell count, platelet count, mean platelet volume, and serum arachidonic acid raise platelet aggregation.
Mutanen et. al. 1995	Cross-sectional study; 204 finnish participants aged 15-30; Dietary factors	Platelet aggregation with ADP and collagen showed that the diet characterized as 'saturated', i.e. containing high-fat milk and saturated fat, was associated with platelets less sensitive to aggregating agents in vitro when compared to the unsaturated type of diet. Collagen-but not ADP-induced aggregation decreased with age of the subjects (P = 0.026–0.057, regression coefficient
Prakash et. al. 1994	Prakash et. al. 1994; Controlled clinical trial; 9 healthy males; 450g/ day Salmon, normal diet	In vitro generation of thromboxane B2 in response to collagen-stimulated aggregation of platelet-rich plasma from subjects consuming the salmon diet was reduced (1.87 ± 0.79 ng/mL) compared with subjects consuming the reference diet (3.10 ± 1.81 ng/mL).
Beswick et. al. 1991	Secondary analysis of RCT; 56 men who had sustained one or more myocardial infarction; Advice to eat fatty fish on at least 2 days each week, Advice to reduce total fat intake	The amount of fat consumed (estimated as the percentage of total energy intake) did not appear to be associated with any of the platelet tests. However, the dietary polyunsaturated fat: saturated fat (P:S) ratio showed a marked correlation with secondary platelet aggregation to ADP in PRP. This varied from 50% of men who showed high activity in the lowest P:S group, to 0%) in the highest P:S group (Mantel-Haenszel Chi-square trend = 8.20. P = 0.004)
Silbert et. al 1990	Single blinded, placebo controlled crossover trial; 9 healthy males; 1500 iu/day of D-a-tocopherol in three divided doses for 14 days, placebo	There were no significant differences (P> 0.05) between baseline, placebo and vitamin E treatment periods in either whole blood or PRP
Honstra et. al. 1990	RCT; 84 healthy males; 135g mackerel paste/day, 135g meat paste/day	HHT from arachidonic acid (AA) clearly reduced in the mackerel group, whereas the formation of HHTE from timnodonic acid (TA) increased slightly. Changes in the formation of HHT and HHTE, measured by HPLC, correlated significantly with those of TxB2 and TxB3, respectively, measured by GCIMS. Changes in the formation of the lipoxygenase products HETE (ex AA) and HEPE (ex TA) were qualitatively similar to that seen for the cyclo-oxygenase products, but quantitatively the responses were smaller. Formation of TxB2 in clotting blood significantly reduced in the mackerel group. In collagen-activated, titrated whole blood, TxB2 formation tended to be reduced in the mackerel-supplemented volunteers.
Croset et. al. 1990	RCT; 16 elderly participants; 100mg Eicosapentaenoic acid (EPA); 100mg Vitamin E	Epinephrine and AA-induced aggregations were significantly inhibited after EPA intake for low concentrations of epinephrine (0.5 BM) and AA (0.225 PM), this inhibition being reversed for higher inducer concentrations. Epinephrine- and AA-ED50 were increased after EPA intake, but, neither the percentage of aggregations nor the ED50 were changed when ADP and collagen were used as aggregating agents. Thrombin-induced aggregation was lower in EPA-treated subjects (p = 0.07) as shown by the increase of ED50, but that induced by U-46619 was left unchanged; and AA- and collagen-ED50 were not significantly different.
Van Houwelingen et. al. 1989	RCT; 20 healthy males; 135g mackerel paste/day, 135g meat paste/day	No significant differences exist between the mackerel- and the control group. The same holds for the other aggregation variables and the results of the ATP release
Seiss et. al. 1980	Longitudinal study; 7 healthy white males; Mackerel diet	In vitro platelet aggregation and TXB2 formation induced by low doses of collagen were significantly reduced. The reduction of platelet aggregation correlated with diminished TXB2 formation and was dependant on the C20:5/C20:4 ratio in platelet phospholipids. Platelet aggregation after l-adrenaline, and the concurrent TXB2 formation as well as the TXB2 formation after high dose collagen decreased, however these differences did not reach significance. ADP-induced platelet aggregation tended to decrease but to a significant level only in some subjects. Platelet aggregation and TXB2 synthesis induced by exogenous arachidonic acid were not changed.
Seyberth et. al. 1975	Longitudinal study; 4 males; Ethyl arachidonate, Placebo	The threshold concentration of ADP necessary to induce the secondary irreversible aggregation of PRP dropped significantly in all 4 volunteers

Changes in platelet aggregation significantly different from control were found in 5 studies. Dietary factors found to be significant were: dark chocolate; energy drinks; dietary nitrate; aged garlic extract; high saturated fat diet; flavanoid rich diet.

Innes et. al. investigated the effect on platelet aggregation by dark chocolate, building on previous work showing the cardioprotective effect of foods rich in flavonoids [5]. Their randomised control trial (RCT) randomised participants to 100g of white chocolate, milk chocolate or dark chocolate. White chocolate contained no cocoa so therefore served as the control. They found that dark chocolate participants had a statistically significant reduction in overall platelet aggregation and rate of aggregation when stimulated by both 0.5ul/mg & 1.0ul/mg collagen. There was no reported reduction in platelet aggregation with ADP stimulation. This would appear to fit with the previously published literature.

Cocoa has been shown to be rich in polyphenols (flavonoids being a member of this class) and a previous study showed its effect in reducing both stimulated and unstimulated platelet activation in vitro and ex vivo [6].

Worthley et. al. found that energy drink consumption increased the overall extent of platelet aggregation (measured by aggregometry) in

response to both lower and higher levels of ADP stimulation (1 umol/L and 10 umol/L respectively) when compared to baseline values. Unfortunately, a recognised limitation of this study is that it leaves the question open around which ingredient in the energy drink may be responsible for this observed effect. Possible causative agents include caffeine, taurine and glucuronolactone. Although, majority of papers on caffeine suggest it decreases/has no effect on platelet activation (at rest or following stimulation). Glucuronolactone is the least studied in terms of platelet function. Further studies are therefore required to identify if this effect can be replicated with any of the individual constituents of energy drinks.

Interestingly, in response to dietary nitrate supplementation, one study found differences in platelet aggregation responses between genders. With male subjects having a reduction of platelet aggregation induced by both ADP and collagen with dietary nitrate supplementation. Female subjects did not have this reduction in platelet aggregation induced by ADP, collagen or epinephrine. Also observed in this study, incubation of PRP with nitrate did not cause a reduction in platelet aggregation in PRP but incubation of the whole blood sample with nitrite lead to a statistically significant reduction in platelet aggregation as measured by whole blood impedance aggregometry [7].

Garlic has also been implicated as a dietary agent which can reduce platelet aggregation and have cardioprotective effects. Rahman and Billington (2000) found that "The extent of platelet aggregation in response to ADP was reduced" after dietary supplementation with 5 mL of aged garlic extract over 13 weeks. The rate of platelet aggregation was statistically significantly reduced compared to baseline measurements - 2.84 +/- 0.25 (1.94 +/- 0.22) p = 0.0066. The overall maximum platelet aggregation was unaffected however.

Drugs and Platelet Function: In addition to drugs used specifically for their anti-platelet activity, some other drugs have been shown to reduce platelet activation. Through this literature search ketorolac, propacetamol and magnesium have been shown to reduce platelet activation [8, 9]. These are potential agents which can be advised against use if possibly for a period prior to PRP collection and therapy in addition to advise against traditional anti-platelet therapy such as aspirin and clopidogrel.

Cyclosporin A has been shown to increase platelet aggregation among healthy volunteers compared with baseline [31]. Whether this knowledge can be used therapeutically is unknown as the risk of thromboembolic events with increased platelet activation has to be considered.

Discussion

This review found some evidence regarding platelet aggregation and activation and patient factors, with the majority examining dietary effect on platelet function. Among this, most of the evidence found foods which reduced platelet activity. From this there are some foods which should be advised to be reduced in diet prior to PRP collection and therapy in order to give the greatest chance for maximum platelet activation. These foods would be dark chocolate, foods high in nitrates, foods high in saturated fats, foods high in garlic. Only energy drink consumption was found to increase platelet aggregation, although the causative ingredient cannot be specified. Further pilot studies may be necessary to examine effect using individual constituents of energy drinks.

The evidence surrounding exercise and platelet function is inconclusive. Although, it would suggest that in the short-term exercise can increase platelet counts and platelet aggregation. Again, we suggest that this effect be studied in further updated pilot studies where platelet count, aggregation and growth factors are measured.

Following this literature search, we suggest that ketorolac, propacetamol and magnesium be added to drugs which are advised against if possible, prior to PRP collection due to anti-platelet activity. Whether drugs such as cyclosporin A can be used to increase platelet activity will have to be considered in clinical trials where safety outcomes are thoroughly assessed.

Much of these conclusions rely on the measure of platelet aggregation as being predictive of effect of PRP. It has not been conclusively shown that maximal platelet aggregation correlates to maximal release of growth factors from platelets. Quantification of levels of growth factors, platelet counts and inducible platelet aggregation and their correlation to clinical outcomes with PRP use still needs to be confirmed by high quality randomised control trials with good reporting of methodology.

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