Annals of
Reviews and Research

Juniper Publishers
key to the Researchers

Review Article
Volume 10 Issue 2 - October 2023
DOI: 10.19080/ARR.2023.10.555782

Ann Rev Resear


# Dietary Factors Influencing Platelet Counts: Knowledge to Improve Concentration for Platelet-Rich Plasma Injections

**Idris Amin*, Swathi Muttana, Dana Dhami, Sarah Cassatt**

*University of Maryland School of Medicine, Baltimore, MD*

**Submission**: October 04, 2023; **Published:** October 16, 2023

***Corresponding author:** Idris Amin, University of Maryland School of Medicine, Baltimore, MD

**Abstract**

The use of biologics, such as platelet-rich plasma (PRP) injections, has been widely used in the healing process surrounding injuries. Given the growth factor-rich property in nature, PRP injections induce neovascularization significantly. There has been research surrounding the role of diet and nutrition on platelet count and function. States of iron deficiency and dyslipidemia have supporting evidence of increasing platelet count. In contrast, ketogenic diets, cod liver, and vitamin D have been associated with decreased platelet counts. Considering that both diet and nutrients affect platelets, perhaps using this theory could be further researched in providing higher-quality PRP injections.

**Keywords:** Platelets; Platelet Count; Platelet Production; Platelet Function; Thrombopoiesis; Thrombopoietin; Diet; Nutrition; Platelet-rich Plasma

## Introduction

There are nearly one trillion platelets in the circulation of an adult that function primarily as hemostatic regulators, and secondarily in innate immunity and angiogenesis. These anucleate, discoid-shaped cells are produced from megakaryocytes that primarily reside in the bone marrow; however, the mechanisms involved in platelet production are poorly understood [1,2]. While this mechanism is poorly understood, the utilization of platelet-rich plasma (PRP) has been a modality in various regenerative medicine management for over 30 years [3]. The mechanism of PRP therapy is believed to be that the injection of concentrated platelets can potentially initiate tissue repair at the site of injury through the release of biologically active factors along with adhesions proteins that are accountable in the coagulation cascade, revascularization, and synthesizing connective tissue. Current research is in support of the PRP concentrates stimulating the physiological release of biologically active growth factors to accelerate the healing process [4]. Within reason, there is a positive correlation between platelet counts and the outcome of PRP injections. Considering there is variability between patients and their platelet count, the underlying question of how patients can increase their platelet count should be further investigated. One mechanism we believe to increase platelet counts is through both diet and nutritional factors, while this concept has been poorly explored. We will discuss the influence of diet and nutrition and their effects on platelet count from what current research has exhibited in hopes to relate this to achieve higher quality PRP injections.

## Discussion

### Platelet Production

**Megakaryopoiesis**: Megakaryopoiesis is a process required for platelet production as megakaryocytes are the source of platelets. Megakaryocytes are a small component of the myeloid lineage, and primarily reside in the bone marrow, but may also be found in the peripheral blood and lungs [5]. During fetal development, megakaryopoiesis occurs within the fetal yolk sac and liver, prior to the enlargement of marrow cavities sufficiently supporting blood cell development [6]. Megakaryocytes are derived from pluripotent hematopoietic stem cells (HSCs), which create both colony-forming cells and burst-forming cells [7]. Both cell types continue through their lineage, which subsequently forms megakaryocyte precursors, creating what we know today as megakaryocytes and the source of platelets [5].

### The Regulation and Function of Thrombopoietin in Platelet Production

The formation of platelets, known as thrombopoiesis, requires regulators and transcription factors. The primary regulator of

thrombopoiesis called thrombopoietin (TPO), is known to affect every stage of thrombopoiesis between an interplay of both extrinsic and intrinsic influences on hematopoiesis [8]. The relationship of TPO levels in the bone and marrow is largely theorized to be inversely proportional to platelet count [9]. Receptor-mediated uptake and destruction is a major component in TPO regulation and is controlled via hematopoietic growth factor regulation. An autoregulatory loop is maintained by platelets that have a high affinity towards TPO receptors, thus removing TPO from the circulation in states of thrombocytosis, subsequently resulting in a decrease of platelet production. In contrast, this autoregulatory loop is maintained during states of thrombocytopenia, to prevent platelet production [10].

## Platelet Function

**Hemostasis and Thrombosis:** The function of platelets has been long theorized to aid in primary hemostasis and blood flow within the vessel [11,12]. The platelets flow through the vessel, staying adjacent to the vessel wall, allowing for quick activation at the time of vascular injury or insult. This activation is thought to occur in several steps, beginning with endothelial or subendothelial matrix attachment. Next, the platelets firmly adhere to the matrix, flatten, and subsequently undergo intraplatelet signal transduction, which forms the initial clot or thrombus formation. This initial platelet plug forms a core at the site of injury that is densely packed, fibrin rich, and P-selectin positive. Following the initial platelet plug formation, loosely associated platelets and circulating platelets become activated via COX-1, 12-LOX, and granule secretions. This entire process results in a platelet thrombus consisting of a tightly packed core of P-selectin positive platelets with a surrounding shell of loosely packed platelets [13-15].

**Bioactive Mediators and the Use of Platelet-Rich Plasma in Injuries:** Platelet-rich plasma (PRP) injections utilize bioactive mediators to provide repair and relief in injury processes. It is reported that 30% of musculoskeletal presenting complaints are secondary to tendon injury [16]. The tendon repair process is both slow and tissue repair frequently relates to re-injury due to the tendon's poorly vascular nature [17]. Angiogenesis partakes in several roles of tendon healing and is considered to be one of the earliest events of tendon healing. This event allows for the delivery of inflammatory cells and fibroblasts to be delivered to the site of trauma via neovascularization [18]. Additional roles of angiogenesis include oxygen and nutrient delivery, removal of waste products, controlling immune response, and the transportation of regulatory factors [19].

Another strong association of overcoming tendon injury involves growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor-B (TGF-B), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Platelets secrete alpha granules following tendon injury which results in the release of these growth factors [20]. Notably, VEGF is considered to be the most important factor in promoting angiogenesis, improving fibroblast proliferation, and in the initiation of producing other growth factors [16]. There has been much research surrounding tendon healing and biologics to assist in the healing process. Tendon repair is associated with both intrinsic and extrinsic repair mechanisms and is separated into inflammation, proliferation, and remodeling phases [21]. The extrinsic healing process is regulated by substances originating from the outside of the tendon and involves plasma, fibroblasts, inflammatory cells, and extra-tendinous vascular invasion. The intrinsic healing process occurs due to the activity of tenocytes and intratendinous blood supply within the tendon itself [22]. PRP is known to be rich in growth factors allowing for assistance with tendon repair. Research studies have compared PRP compared to a placebo and revealed PRP induced neovascularization significantly [17]. These findings in combination with known bioactive mediator processes are suggestive of PRP injections being beneficial.

**Immunogenic Role:** Recent literature has proposed that one role of the platelet is associated with immunologic processes, however it is still unclear. The study proposed that autophagy may be exhibited by platelets, yet the mechanism is still unclear. Another study proposed that platelets express all nine toll-like receptors (TLRs), which allows for further research to observe the role platelets play in relation to innate immunity against bacteria, viruses, and pathological processes such as tumors [23,24].

## Factors Increasing Platelet Count

TPO is the main regulator in thrombopoiesis, however, it has been found that variation in diet and nutrition can increase and decrease platelet levels. In a review of the literature, Alpha-linolenic acid (ALA), hypercholesterolemia, and iron deficiency anemia have all been associated with increased platelet counts.

While dietary ALA is known to be anti-inflammatory, anti-atherosclerotic, and have anti-platelet effects, a study by Stivala et al. showed an ALA-induced increased platelet count in ApoE -/- mice. The increase in platelets can be explained by reduced platelet clearance. ALA reduces the clearance of platelets by reducing platelet turnover and activation via TACE-mediated CPib cleavage via inhibition of p38 [25]. Megakaryopoiesis is stimulated by hypercholesterolemia resulting in platelet production [26]. The mechanism by which hypercholesterolemia causes increased platelet formation, turnover, and activation is not well understood; however, there is a positive correlation between non-HDL cholesterol levels with platelet counts as seen in 2 independent studies involving 10,000 participants [27].

Iron deficiency causes both a decrease in hemoglobin and reactive thrombosis. Maintaining thrombocytosis in iron deficiency is thought to be due to maintaining coagulation in situations such as chronic bleeding, however the mechanism of thrombocytosis


How to cite this article: Idris A, Swathi M, Dana Dhami, Sarah C. Dietary Factors Influencing Platelet Counts: Knowledge to Improve Concentration for Platelet-Rich Plasma Injections. Ann Rev Resear. 2023; 10(2): 555782. DOI:10.19080/ARR.2023.10.555782

in iron deficiency is still unknown. Evstatiev et al. found that iron deficiency leads to megakaryopoiesis differentiation and changes in platelet phenotype without any influence on TPO in animal models. Independent of TPO, Bone marrow changes in iron deficiency showed an increase of hematopoietic progenitors to megakaryocytes as well as accelerated megakaryocyte differentiation. Platelets in iron deficiency are greater in number, larger, and have increased aggregation capabilities; all of which were independent of TPO [28].

### Factors Normalizing Platelet Count

While hypercholesterolemia, iron deficiency, and ALA are all associated with increased platelet counts, the Mediterranean diet is associated with the normalization of platelet levels from elevated levels while also reducing the risk of thrombocytopenia. The Mediterranean diet consists of plant-based foods, whole grains, fish, legumes, and olive oil. These foods are high in antioxidants, fiber, monounsaturated fatty acids, and polyunsaturated fatty acids and are associated with a reduction in inflammation via antioxidants and polyphenols. A balanced ratio of w-6 and w-3 essential acids have beneficial effects on both cardiovascular and cerebrovascular health. Platelets and WBC are markers of inflammation and increase the risk for cardiovascular and cerebrovascular disease. The Moli-sani study showed a significant reduction in platelet and WBC counts in the Mediterranean diet in a healthy adult population while controlling for many possible confounders [29]. Additional studies have found a relationship between the mediterranean diet and platelet counts. In a random controlled trial by Hernáez et al., the Mediterranean diet was found to help maintain platelet counts within a normal range in elderly patients with high cardiovascular risk. In both the general population and high cardiovascular-risk individuals, elevated platelet counts are associated with increased mortality and incidence of cardiovascular disease. Additionally, the Mediterranean diet decreases the risk of developing thrombocytopenia in older adults with high cardiovascular risk and reduces all-cause mortality risk [30].

### Factors Decreasing Platelet Count

Ketogenic diets, cod liver, and vitamin D have all been associated with a decrease in platelet count. In a 1,2399-participant observational study by Kucukay and Alanli, platelet counts were significantly lower in hospital patients receiving vitamin D replacement treatments [31]. The mechanism by which vitamin D reduces platelet counts is not well understood but should still be considered. A study by Dressler Et. Al revealed mild thrombocytosis in epileptic pediatric patients at baseline which subsequently normalized while on a ketogenic diet in all patient groups within 6 months. The baseline elevation in platelet count in the epileptic population is thought to be due to underlying inflammation [32]. The ketogenic diet has been shown to have anti-inflammatory properties by reducing IL-8 Beta levels in the brain and plasma [33].

Supplementation of w-3 polyunsaturated fatty acids, as found in cod liver oil, was associated with decreased platelet count and function. In a study by Lorenz Et Al., Eight volunteers were provided with 40 ml of cod liver oil for 25 days which lead to w-3 polyunsaturated fatty acids being incorporated in platelet phospholipids instead of the more common w-6 polyunsaturated fatty acids found in Western diets [34]. Supplementation with n-3 fatty acids or marine oils can reduce the platelet content of arachidonic acid and compete with arachidonic acid for cyclooxygenase, which reduces the production of thromboxane, this leads to decreased platelet aggregation and prolonged bleeding time [35]. While dietary influence on platelet counts is not a well-researched area, there is a potential for further research and treatments of various platelet-related pathologies.

## Conclusion

Based on our research, states of iron deficiency and dyslipidemia have supporting evidence of increasing platelet count. In contrast, ketogenic diets, cod liver, and vitamin D have been associated with a decrease in platelet counts. While there is limited research currently on this topic, these findings should be executed by restricting ketogenic diets, cod liver, and excess vitamin D rather than inducing iron deficiency and hypercholesterolemia that pose unethical and detrimental effects. Dietary restriction prior to a procedure could be suggested, while more data needs to be collected prospectively to assess whether patients had better outcomes with the PRP injections.

## References

1. Thon JN, Italiano JE (2012) Platelets: production, morphology, and ultrastructure. Handb Exp Pharmacol 210: 3-22.
2. Thon JN, Italiano JE (2010) Platelet formation. Semin Hematol 47(3): 220-226.
3. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K (2020) Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. Int J Mol Sci 21(20): 7794.
4. Everts PA, Knape JT, Weibrich G, Schönberger JP, Hoffmann J, et al. (2006) Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol 38(2): 174-187.
5. Ogawa D (1993) Differentiation and proliferation of hematopoietic stem cells. Blood 81(11): 2844-2853.
6. Patel SR, Hartwig JH, Italiano JE Jr (2005) The biogenesis of platelets from megakaryocyte proplatelets. J Clin Invest 115(12): 3348-3354.
7. Briddell RA, Brandt JE, Strana JE, Srour EF, Hoffman R (1989) Characterization of the human burst-forming unit-megakaryocyte. Blood 74(1): 145-151.
8. Kaushansky K (2005) The molecular mechanisms that control thrombopoiesis. J Clin Invest 115(12): 3339-3347.
9. Shinjo K, Takeshita A, Nakamura S, Naitoh K, Yanagi M, et al. (1998) Serum thrombopoietin levels in patients correlate inversely with platelet counts during chemotherapy-induced thrombocytopenia. Leukemia 12(3): 295-300.
10. Kuter DJ, Rosenberg RD (1995) The reciprocal relationship of thrombopoietin (c-Mpl ligand) to changes in the platelet mass during busulfan-induced thrombocytopenia in the rabbit. Blood 85(10): 2720-2730.


How to cite this article: Idris A, Swathi M, Dana Dhami, Sarah C. Dietary Factors Influencing Platelet Counts: Knowledge to Improve Concentration for Platelet-Rich Plasma Injections. Ann Rev Resear. 2023; 10(2): 555782. DOI:10.19080/ARR.2023.10.555782

11. Tomaiuolo M, Brass LF, Stalker TJ (2017) Regulation of Platelet Activation and Coagulation and Its Role in Vascular Injury and Arterial Thrombosis. Interv Cardiol Clin 6(1): 1-12.

12. Jackson SP (2011) Arterial thrombosis--insidious, unpredictable, and deadly. Nat Med 17(11): 1423-1436.

13. Stalker TJ, Traxler EA, Wu J, Wannemacher KM, Cermignano SL (2013) Hierarchical organization in the hemostatic response and its relationship to the platelet-signaling network. Blood 121(10): 1875-1885.

14. Welsh JD, Muthard RW, Stalker TJ, Taliaferro JP, Diamond SL, et al. (2016) A system's approach to hemostasis: 4. How hemostatic thrombi limits the loss of plasma-borne molecules from microvasculature. Blood 127(12):1598-1605.

15. Welsh JD, Stalker TJ, Voronov R, Muthard RW, Tomaiuolo M, et al. (2014) A system's approach to hemostasis: 1. The interdependence of thrombus architecture and agonist movements in the gaps between platelets. Blood 124(11): 1808-1815.

16. Liu X, Zhu B, Li Y, Liu X, Guo S, et al. (2021) The Role of Vascular Endothelial Growth Factor in Tendon Healing. Front Physiol 12: 766080.

17. Bosch G, Moleman M, Barneveld A, van Weeren PR, van Schie HT (2011) The effect of platelet-rich plasma on the neovascularization of surgically created equine superficial digital flexor tendon lesions. Scand J Med Sci Sports 21(4): 554-561.

18. Petersen W, Pufe T, Unterhauser F, Zantop T, Mentlein R, et al. (2003) The splice variants 120 and 164 of the angiogenic peptide vascular endothelial cell growth factor (VEGF) are expressed during Achilles tendon healing. Arch Orthop Trauma Surg. 123(9): 475-480.

19. Nakamura K, Kitaoka K, Tomita K (2008) Effect of eccentric exercise on the healing process of injured patellar tendon in rats. J Orthop Sci 13(4): 371-378.

20. Petersen W, Pufe T, Unterhauser F, Zantop T, Mentlein R, et al. (2003) The splice variants 120 and 164 of the angiogenic peptide vascular endothelial cell growth factor (VEGF) is expressed during Achilles tendon healing. Arch Orthop Trauma Surg. 123(9): 475-480.

21. Wu PI, Diaz R, Borg-Stein J (2016) Platelet-Rich Plasma. Phys Med Rehabil Clin N Am 27(4): 825-853.

22. Zhang F, Liu H, Stile F, Lei MP, Pang Y (2003) Effect of vascular endothelial growth factor on rat Achilles tendon healing. Plast Reconstr Surg 112(6): 1613-1619.

23. Ouseph MM, Huang Y, Banerjee M, Joshi S, MacDonald L (2015) Autophagy is induced upon platelet activation and is essential for hemostasis and thrombosis. Blood 126(10): 1224-1233.

24. Koupenova M, Mick E, Mikhalev E, Benjamin EJ, Tanriverdi K (2015) Sex differences in platelet toll-like receptors and their association with cardiovascular risk factors. Arterioscler Thromb Vasc Biol 35(4): 1030-1037.

25. Stivala S, Reiner MF, Lohmann C, Lüscher TF, Matter CM (2013) Dietary α-linolenic acid increases the platelet count in ApoE-/- mice by reducing clearance. Blood 122(6): 1026-1033.

26. Tanczos B, Somogyi V, Bombicz M, Juhasz B, Nemeth N (2021) Changes of Hematological and Hemorheological Parameters in Rabbits with Hypercholesterolemia. Metabolites 11(4): 249.

27. Nan Wang, Alan R Tall (2016) Cholesterol in platelet biogenesis and activation. Blood 127 (16): 1949-1953.

28. Evstatiev R, Bukaty A, Jimenez K, Kulnigg-Dabsch S, Surman L (2014) Iron deficiency alters megakaryopoiesis and platelet phenotype independent of thrombopoietin. Am J Hematol 89(5): 524-529.

29. Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Persichillo M (2014) Moli-sani Project Investigators. Adherence to the Mediterranean diet is associated with lower platelet and leukocyte counts: results from the Moli-sani study. Blood 123(19): 3037-3044.

30. Hernáez Á, Lassale C, Castro-Barquero S, Tresserra-Rimbau A, Castañer O (2021) Mediterranean Diet Maintained Platelet Count within a Healthy Range and Decreased Thrombocytopenia-Related Mortality Risk: A Randomized Controlled Trial. Nutrients 13(2): 559.

31. Kucukay MB, Alanli R (2021) Vitamin D Replacement Effect on Platelet Counts. J Coll Physicians Surg Pak 31(9):1064-1068.

32. Dressler A, Chiara H, Benninger F, Waldhoer T, Gröppel G (2020) Effects of the ketogenic diet on platelet counts and global coagulation tests in childhood epilepsy. Seizure 80: 31-37.

33. Mathern G, Nehlig A, Sperling M (2015) Interview with Matthew Diamond, 2014 Epilepsia prize winner. Epilepsia, 56: 987-988.

34. Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC (1983) Platelet function, thromboxane formation and blood pressure control during supplementation of the Western diet with cod liver oil. Circulation 67(3): 504-511.

35. George JN, Shattil SJ (1991) The clinical importance of acquired abnormalities of platelet function. N Engl J Med 324(1): 27-39.



DOI:10.19080/ARR.2023.10.555782




**How to cite this article:** Idris A, Swathi M, Dana Dhami, Sarah C. Dietary Factors Influencing Platelet Counts: Knowledge to Improve Concentration for Platelet-Rich Plasma Injections. Ann Rev Resear. 2023; 10(2): 555782. DOI:10.19080/ARR.2023.10.555782