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Acute Fish Oil supplementation and Aspirin treatment modulates lipid profile in Platelet Rich Plasma: a randomized pilot trial

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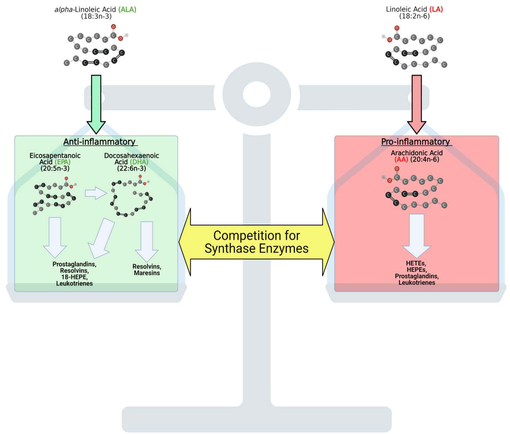
Introduction

Autologous platelet rich plasma (PRP) is a biologic utilized to stimulate the healing of damaged tissues. It is composed of various lipids. One active component to PRP's lipid fraction are eicosanoids, bioactive signaling lipids derived from ω-3 and ω-6 polyunsaturated fatty acids (PUFAs)[1]. Current dogma suggests that ω-3 PUFAs (eg a high ω-3:ω-6 ratio) and its eicosanoids can promote health in humans. This is achieved classically by these eicosanoids acting in autocrine and paracrine circuits[3], prompting lower systemic inflammation by modulation of lymphocyte proliferation and cytokine production[2,3]. These eicosanoids are time sensitive mediators of inflammation synthesized at sites of tissue damage whose dysregulation are associated with pathological tissue repair[1]. While diverse in structure and function, ω-3 and ω-6 derived eicosanoids share common enzymatic pathways like the cyclooxygenase (COX) pathway and therefore compete.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin modulate eicosanoids by inhibiting their aforementioned proinflammatory COX pathway, triggering aspirin-specialized proresolving lipid mediator production pathways[3]. The ratio or "balance" of proinflammatory and proresolving lipids are dependent in part on the availability of their precursor lipids[1]. These lipids' bioavailability in the blood and their efficacy for clinical use are current, ongoing areas of research[1,3]. We investigated whether the short-term alteration of the ω-3/ω-6 ratio led to the production of PRP with a more proresolving lipid profile. Granted the diversity of these lipid species, the relative abundance of eicosanoids and their precursors must be measured when assessing outcomes, rather than the mere presence or absence of a lipid species[1,3].



Methods

Platelet rich plasma (PRP) at baseline and 6-hours was collected from 47 patients randomly assigned to either placebo, one soft-gel Fish oil tablet (1400 mg, Sundown Naturals, NY), Bayer low-dose aspirin (81mg), or combinational therapy. Targeted analysis of eicosanoids and select PUFAs was conducted by liquid chromatography tandem mass spectrometry via a TripleTOF 6600 mass spectrometry paired to an Agilent 1290 liquid chromatograph (LC). Remaining lipids were acquired by direct infusion via a 5600+ TripleTOF mass spectrometry (ScieX). Eicosanoids were normalized as a ratio of area to their internal standard; all lipids other than eicosanoids were expressed as mol%. Data were log transformed and Pareto scaled to correct for variances in lipid class abundance. Outliers were detected by the 1.5 x the interquartile range (IQR) and winsorized within treatment groups by 25th and 75th percentiles. One-way analysis of variance (ANOVA) with Tukey's honestly significant difference (Tukey HSD) post-hoc test was performed to determine the interaction of group and time on lipid modulation. FDR-adjustment was performed to correct for multiple testing. Spearman's correlation analysis presented any correlations between PUFAs and major lipid classes against eicosanoids. All analyses were conducted in MetaboAnalyst 5.0, JMP Pro 15.1.0, and in-house R scripts (version 4.0.3).

Results

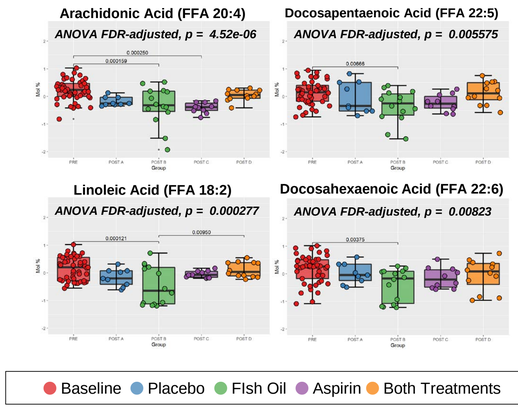


Figure 1: Comparisons of PRP PUFAs demonstrate modulation after 6 hours of fish oil treatment and aspirin. Precursor ω-6 linoleic acid (FFA 18:2) and derivative arachidonic acid (FFA 20:4) were reduced in fish oil. With fish oil supplementation, the ω-6 PUFAs docosahexaenoic acid (FFA 22:6) and docosapentaenoic acid (FFA 22:5) were also reduced. Brackets represent Tukey HSD adjusted p-values.

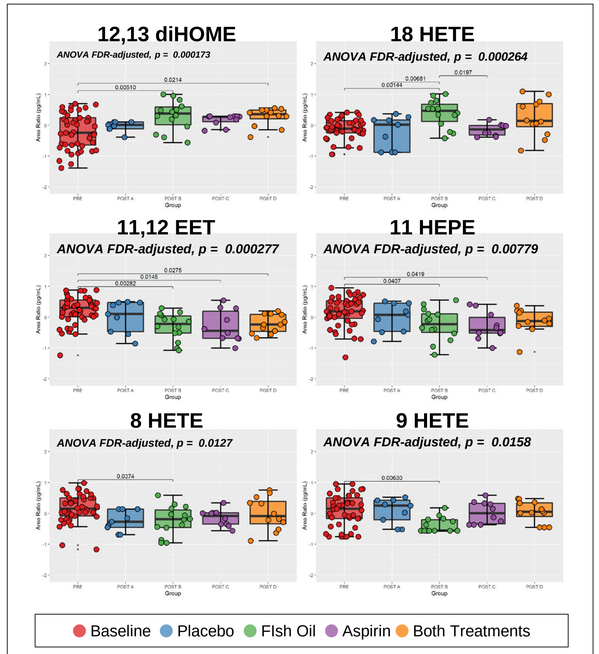


Figure 2: Comparisons of PRP eicosanoids demonstrates modulation after 6 hours of fish oil treatment and aspirin. These oxylipins and other and other ω-6 derivatives were differentially modulated by supplementation of fish oil. To note, some lipids were similarly affected in fish oil in aspirin or combinational therapy. Brackets represent Tukey HSD adjusted p-values.

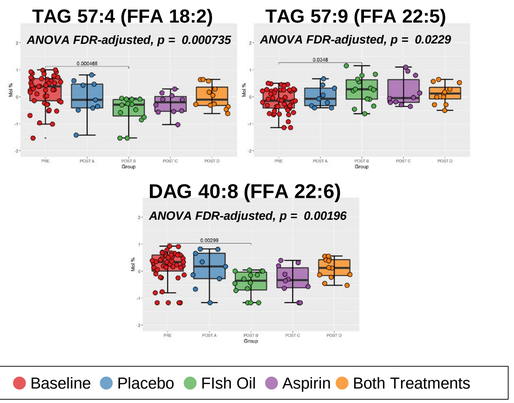


Figure 3: Comparisons of glycerolipid species demonstrates peripheral lipids influenced by Fish Oil treatment. Tri/diacylglycerols involved in ω-3 and ω-6 metabolism offers insight into the flux of bioactive lipids in PRP. Brackets represent Tukey HSD adjusted p-values.

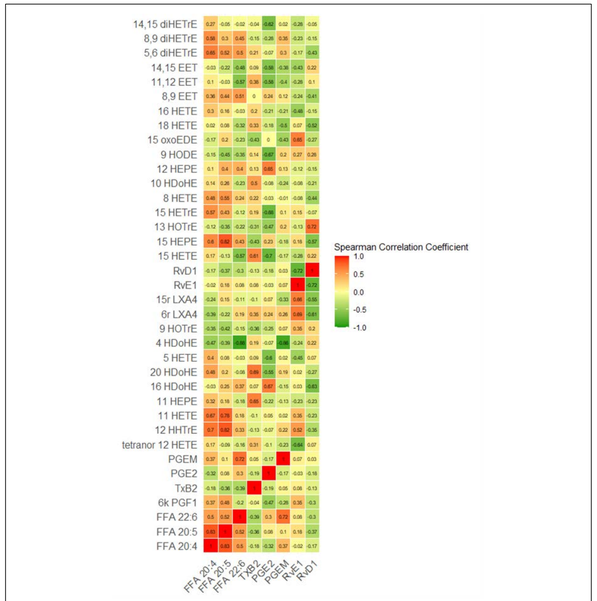


Figure 3: Spearman rank correlation for PUFA into eicosanoids. Correlations reported for fish oil group, cross referenced against control. Correlated PUFAs include ω-6 Arachidonic acid (FFA 20:4), and ω-3 Eicosapentaenoic acid (FFA 20:5) and Docosahexaenoic acid (FFA 22:6).

Conclusions

This prospective study demonstrates that short-term or acute administration of PUFAs can yield exogenous, modulatory effects on PRP's lipid fraction. A pronounced fluctuation in circulatory ω-6 PUFAs and their derivatives, such as those within the oxylipin profile (eg 12,13 diHOME and 11,12 EET), occurred in the fish oil treatment group with some similarities observed in the aspirin and combinational therapy groups. When compared to the control's correlations, inverse correlations were observed in the fish oil treatment group between ω-6 PUFA arachidonic acid (FFA 20:4) and prostaglandins, resolvins, and thromboxanes. Quantification of ω-3, ω-6 PUFAs, and their metabolites offers an insightful snapshot of the biologically available lipids following supplementation. Larger future studies that leverage varying doses of fish oil, and further explores these underlying mechanistic pathways, could evaluate the efficacy of PRP therapy. These studies would support a comprehensive framework to further optimize PRP for treatment of inflammatory diseases.

References

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