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The Relationship Between Aspirin and Vitamin D: Current Evidence and Mechanisms

The intersection of aspirin and vitamin D pathways represents an intriguing area of research with potential implications for various health conditions. This report examines whether aspirin increases vitamin D levels or enhances vitamin D receptor (VDR) activation based on current scientific evidence.

Understanding Vitamin D and Its Receptor

Vitamin D is a fat-soluble secosteroid linked to calcium homeostasis and bone metabolism that may also possess antiproliferative properties[1]. The biological actions of vitamin D, particularly its active form 1,25-dihydroxyvitamin D (calcitriol), are mediated through the vitamin D receptor (VDR), a nuclear transcription factor belonging to the nuclear hormone receptor superfamily[2][3]. Upon binding to the active form of vitamin D, VDR translocates from the cytoplasm into the nucleus and binds to vitamin D responsive elements (VDREs), regulating the expression of numerous genes involved in various physiological processes[3].

Evidence on Aspirin's Effects on Vitamin D Levels and VDR Activation

Current research does not provide strong evidence that aspirin directly increases vitamin D levels or enhances VDR activation. In fact, some studies suggest more complex interactions between these compounds.

Potential Inhibitory Effects

Contrary to the hypothesis that aspirin might increase vitamin D levels or VDR activation, some research suggests possible inhibitory effects. An early study found that aspirin, acting as a prostaglandin biosynthesis inhibitor, abolished hypercalcemia induced by 1-alpha-hydroxyvitamin D3 in various rat models[4]. This finding suggests that aspirin may actually counteract certain effects of vitamin D, particularly those related to calcium metabolism.

Additionally, research on transgenic placental models has shown that low-dose aspirin treatment significantly down-regulates the vitamin D receptor (VDR)[5]. This evidence contradicts the notion that aspirin enhances VDR activation, at least in this specific context.

Relationship Between Vitamin D Status and Aspirin Response

While aspirin may not directly increase vitamin D levels or VDR activation, there appears to be a correlation between vitamin D status and responsiveness to aspirin therapy. A study examining patients with stable coronary artery disease (CAD) found that vitamin D deficiency was associated with aspirin resistance[6] [7]. The study reported that the rate of aspirin resistance was higher in vitamin D-deficient patients compared to those with sufficient vitamin D levels (29% vs. 8%, $p = 0.041$)[6].

In this study, patients with 25-hydroxyvitamin D [25-(OH)D] levels below 20 ng/dl were defined as vitamin D deficient. The mean 25-(OH)D level was lower in the aspirin-resistant group than in the aspirin-sensitive group[7]. This suggests that adequate vitamin D levels may be important for optimal aspirin effectiveness, rather than aspirin increasing vitamin D levels.

Combined Therapeutic Applications

Despite the lack of evidence for aspirin directly increasing vitamin D levels or VDR activation, several studies have investigated the combined therapeutic effects of these compounds.

Cancer Treatment and Prevention

Research on oral squamous cell carcinoma (OSCC) cell lines demonstrated that aspirin and vitamin D3 in combination had synergistic or additive effects against cancer cells. The combination treatment significantly decreased cell proliferation rates and caused higher rates of cell apoptosis compared to either agent alone[8]. This suggests potential benefits of combined therapy, even if they don't directly enhance each other's primary mechanisms.

In prostate cancer research, a feasibility study (PROVENT) investigated aspirin and/or vitamin D3 in men with prostate cancer on active surveillance. The study found that both low-dose (100 mg) and standard-dose (300 mg) aspirin, as well as vitamin D (4000 IU), were well-tolerated separately and in combination[1] [9]. However, the study did not specifically address whether aspirin increased vitamin D levels or VDR activation.

Another study examining tyrosine kinase inhibitor (TKI) therapy for EGFR, ALK, and ROS-positive non-small cell lung cancer found that concurrent use of vitamin D supplementation with TKI prolonged progression-free survival by 16 months versus 11 months ($p = 0.04$)[10]. However, similar benefits were not observed with aspirin or metformin use, suggesting specific pathways for vitamin D effects independent of aspirin.

Bone Metabolism

Research on bone marrow stromal cells (BMSCs) has shown that low-dose aspirin (particularly at 1 mmol/L) increases alkaline phosphatase (ALP) activity, promotes calcification, and affects the osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B ligand (RANKL) system[11]. This suggests potential benefits for bone metabolism, though the relationship to vitamin D pathways was not directly addressed in this study.

Genetic Factors Influencing VDR and Aspirin Effects

Genetic variations in both vitamin D-related genes and aspirin-metabolizing genes may influence their individual and combined effects. Polymorphisms in the VDR gene, including FokI, BsmI, ApaI, and TaqI variants, have been associated with differences in VDR expression and potentially with response to vitamin D[12] [3].

The expression of VDR in tumor tissues has been studied as a potential biomarker for cancer prognosis and treatment response. In melanoma, VDR expression may have implications for vitamin D resistance in tumor tissues and could potentially modulate effects of vitamin D supplementation in prevention therapy[3].

Similarly, genetic variations in catechol-O-methyltransferase (COMT) may modify the cardiovascular benefit of aspirin, suggesting that genetic factors play important roles in determining how patients respond to both vitamin D and aspirin[13].

Conclusion

Based on the available evidence, there is no clear indication that aspirin directly increases vitamin D levels or enhances vitamin D receptor activation. Some research actually suggests potential inhibitory effects on certain vitamin D pathways or VDR expression in specific contexts. However, vitamin D status appears to influence aspirin effectiveness, particularly in cardiovascular applications, suggesting some interrelationship between these pathways.

The combined use of aspirin and vitamin D has shown potential therapeutic benefits in various conditions, particularly in cancer treatment and prevention. These benefits appear to be due to complementary or synergistic effects rather than direct enhancement of vitamin D levels or VDR activation by aspirin.

Further research is needed to fully understand the complex interactions between aspirin and vitamin D, including potential molecular mechanisms, contextual factors that may influence their relationship, and how genetic variations may impact their individual and combined effects. Such understanding could lead to more personalized and effective therapeutic strategies utilizing these widely available compounds.

1. https://pmc.ncbi.nlm.nih.gov/articles/PMC9579886/
2. https://www.mdpi.com/1422-0067/25/19/10677
3. https://www.cancerbiomed.org/content/14/2/162
4. https://pubmed.ncbi.nlm.nih.gov/4004906/
5. https://www.nature.com/articles/s41420-019-0170-x
6. https://pmc.ncbi.nlm.nih.gov/articles/PMC9487833/
7. https://amsad.termedia.pl/Association-between-Multiplate-measured-aspirin-resistance-and-vitamin-D-deficiency,142996,0,2.html
8. https://pubmed.ncbi.nlm.nih.gov/29349624/

9. https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-active-surveillance-aspirin-and-vitamin-d-in-men-with-prostate-cancer-provent
10. https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.e20656
11. https://www.ajol.info/index.php/tjpr/article/view/201822/190321
12. https://pmc.ncbi.nlm.nih.gov/articles/PMC5444928/
13. https://hms.harvard.edu/news/aspirins-two-sides