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The Relationship Between Colchicine and Vitamin D Receptor Activation: Evidence and Mechanisms

Colchicine, a widely used anti-inflammatory medication, has complex interactions with vitamin D metabolism and vitamin D receptor (VDR) function. This comprehensive analysis explores the relationship between colchicine and vitamin D, examining whether colchicine increases vitamin D levels or enhances VDR activation based on current scientific evidence.

Colchicine's Mechanism of Action and Clinical Applications

Colchicine is an anti-mitotic agent that primarily functions by disrupting cytoskeletal functions through the inhibition of β-tubulin polymerization into microtubules. This mechanism prevents the activation, degranulation, and migration of neutrophils, contributing to its anti-inflammatory properties. Clinically, colchicine is utilized to treat conditions such as gout and Familial Mediterranean Fever (FMF), and has demonstrated anti-fibrotic and cardiovascular protective effects. The medication exerts these benefits through interfering with the intracellular assembly of inflammasome complexes in neutrophils and monocytes, which mediate the activation of pro-inflammatory cytokines such as interleukin-1β[1].

Recent research has further elucidated colchicine's anti-inflammatory mechanisms, showing its ability to inhibit NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activation and subsequently reduce IL-1β expression. A 2025 study demonstrated that colchicine treatment significantly reduced IL-1β expression in hypoxic cells compared to placebo-treated hypoxic cells, suggesting its potential benefit in ischemic scenarios[2]. This anti-inflammatory action is central to colchicine's therapeutic efficacy, particularly in conditions characterized by excessive inflammatory responses.

Colchicine's Effects on Vitamin D Receptor Translocation

Contrary to enhancing VDR activation, evidence suggests that colchicine may actually interfere with normal VDR function by inhibiting receptor translocation. One significant study demonstrated that 1,25-dihydroxy-vitamin D3 (1,25(OH)2D3), the hormonally active form of vitamin D, induces the translocation of VDR from the nuclear to the microsomal fraction in skeletal muscle cells. This translocation process, which is critical for vitamin D's non-genomic effects, was notably blocked by colchicine treatment[3]. This finding indicates that colchicine disrupts the microtubular transport necessary for proper VDR trafficking within cells, potentially impairing vitamin D signaling pathways.

The authors of this study concluded that microtubular transport plays an essential role in the relocation of the vitamin D receptor, and colchicine's inhibition of this process may have significant implications for understanding the non-genomic effects of vitamin D in various tissues.

This suggests that rather than enhancing VDR activation, colchicine may actually impede certain aspects of vitamin D function through its effects on cellular microtubule networks[3].

Colchicine's Impact on Vitamin D Metabolism and Levels

Research examining vitamin D status in patients treated with colchicine provides further insights into the relationship between colchicine and vitamin D metabolism. In a study of children with Familial Mediterranean Fever, researchers observed that "defects in the microtubular network attributable to colchicine use may reduce vitamin D levels because of increased production of 1,25(OH) vitamin D and 24,25(OH) vitamin D"[4]. This suggests that colchicine's disruption of microtubule function may alter vitamin D metabolism in ways that ultimately lead to reduced circulating vitamin D levels, rather than increased levels.

Furthermore, the authors noted that "colchicine inhibited the functions of intracellular microtubules, which are essential components of the normal genomic response to vitamin D"[4]. This indicates that colchicine may interfere with cellular responses to vitamin D at multiple levels, affecting both vitamin D metabolism and the cellular machinery necessary for vitamin D's genomic effects. These findings provide additional evidence that colchicine does not enhance vitamin D action but may instead compromise normal vitamin D function.

Vitamin D Status in Colchicine-Treated Patients

Clinical studies examining vitamin D levels in patients treated with colchicine have revealed interesting patterns that further illuminate the relationship between colchicine and vitamin D. One notable study compared vitamin D levels between colchicine-responsive and colchicine-resistant FMF patients. The researchers found that mean 25-hydroxy vitamin D (25-OHD) levels were significantly lower in colchicine-resistant patients (9.39 ± 1.00 ng/mL) compared to colchicine-responsive patients (18.48 ± 1.09 ng/mL)[5] [6]. While this does not directly demonstrate that colchicine reduces vitamin D levels, it suggests a complex relationship between vitamin D status and response to colchicine therapy.

The authors of this study proposed that vitamin D deficiency might be a factor in the etiopathogenesis of colchicine resistance and called for further research to evaluate the response to vitamin D replacement in colchicine-resistant FMF patients[6]. This suggests that maintaining adequate vitamin D levels may be important for optimal response to colchicine therapy, particularly in conditions like FMF where colchicine is a mainstay of treatment.

Understanding the VDR Activation Pathway

To fully understand colchicine's potential effects on the vitamin D system, it's important to consider the normal mechanisms of VDR activation. The vitamin D receptor is a nuclear receptor that, when activated by calcitriol (1α,25-dihydroxyvitamin D3), forms heterodimers with retinoid X receptor (RXR) and associates with vitamin D response elements (VDREs) on target genes to regulate gene expression[7] [8]. This process requires intact cellular machinery, including functional microtubules for proper receptor trafficking.

Studies have shown that VDR activation has broad physiological effects beyond calcium homeostasis, influencing immune function, cardiovascular health, and inflammatory

processes[7]. For example, VDR plays important roles in innate immune responses, with activation of Toll-like receptors in human macrophages upregulating the expression of VDR and leading to induction of antimicrobial peptides[7]. Any disruption to normal VDR trafficking and function, such as that potentially caused by colchicine, could therefore have wide-ranging implications for these physiological processes.

Conclusion

Based on the available scientific evidence, colchicine does not appear to increase vitamin D levels or enhance vitamin D receptor activation. Instead, research suggests that colchicine may interfere with normal VDR function by inhibiting receptor translocation through its effects on microtubule structure and function. Studies indicate that colchicine treatment may be associated with altered vitamin D metabolism and possibly reduced vitamin D levels in certain patient populations.

The relationship between colchicine and vitamin D is complex and multifaceted, involving interactions with cellular transport mechanisms essential for VDR trafficking and function. Understanding these interactions is important for optimizing the clinical use of colchicine, particularly in conditions where vitamin D status may influence treatment response. Further research is warranted to fully elucidate the implications of colchicine's effects on vitamin D metabolism and signaling for patient care and to explore potential strategies for mitigating any adverse impacts on vitamin D function.

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