Exploring the Relationship between Cholesterol Synthesis and Vitamin D: Implications and Insight

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ABSTRACT

Cholesterol synthesis and vitamin D metabolism are essential processes in the human body, each with distinct roles in maintaining health and homeostasis. While cholesterol synthesis primarily produces cholesterol, a vital component of cell membranes and a precursor for steroid hormones, vitamin D metabolism contributes to calcium and phosphorus homeostasis, skeletal health, and immune function. Recent research has revealed intricate connections between these pathways, highlighting their interplay and mutual regulation. This review explores the interrelationship between cholesterol synthesis and vitamin D metabolism, elucidating the mechanisms underlying their crosstalk and discussing the implications for health and disease.

Keywords: Cholesterol synthesis, vitamin D metabolism, interplay, regulatory cross-talk, health implications, therapeutic opportunities.

INTRODUCTION

Cholesterol synthesis and vitamin D metabolism are two essential biochemical pathways in the human body, each playing distinct yet interconnected roles in maintaining health and homeostasis. While cholesterol is often associated with cardiovascular diseases, it serves as a crucial structural component of cell membranes, a precursor for steroid hormones, and a modulator of membrane fluidity and permeability. Conversely, vitamin D, traditionally recognized for its role in calcium and phosphorus homeostasis and skeletal health, has emerged as a multifunctional hormone with diverse effects on immunity, cellular proliferation, and gene expression. Historically, these pathways cholesterol synthesis and vitamin D metabolism have been studied independently, with little consideration of their potential interplay. However, recent advancements in molecular biology and biochemical research have revealed intricate connections between them. One notable aspect of their interrelationship lies in the shared precursor molecules and biosynthetic pathways. For instance, both cholesterol synthesis and vitamin D metabolism utilize 7-dehydrocholesterol as a precursor molecule, emphasizing their biochemical interconnectedness. In addition to shared biosynthetic pathways, regulatory crosstalk between cholesterol synthesis and vitamin D metabolism has garnered increasing attention. Cholesterol-enriched membrane microdomains, known as lipid rafts, play a pivotal role in facilitating the localization and activity of enzymes involved in vitamin D synthesis. Conversely, cholesterol levels may influence the expression and function of proteins involved in vitamin D metabolism, providing a feedback mechanism that modulates vitamin D production and activation. Understanding the interplay between cholesterol synthesis and vitamin D metabolism is not merely of academic interest; it holds significant clinical relevance. Dysregulation of these pathways is
implicated in a wide range of health conditions, spanning cardiovascular diseases, metabolic disorders, skeletal abnormalities, and immune dysfunction. The aberrant cholesterol metabolism is associated with atherosclerosis, hyperlipidemia, and neurodegenerative diseases, while vitamin D deficiency is linked to osteoporosis, autoimmune disorders, infectious diseases, and certain cancers. Moreover, the potential therapeutic implications of targeting shared regulatory nodes in cholesterol synthesis and vitamin D metabolism are increasingly recognized.\[5\] Lifestyle modifications, pharmacological interventions, and dietary supplements aimed at optimizing cholesterol levels and vitamin D status offer promising avenues for disease prevention and management.\[6\] For example, statins, cholesterol-lowering medications widely used in the treatment of cardiovascular diseases, have been shown to impact vitamin D metabolism, suggesting a potential dual benefit in managing both cholesterol-related disorders and vitamin D deficiency.\[7\]

**Overview of cholesterol synthesis and vitamin D metabolism**

Cholesterol synthesis is a complex biochemical process essential for various physiological functions in the human body. It primarily occurs in the liver, although other tissues also contribute. The process starts with the conversion of acetyl-CoA to mevalonate, a key intermediate in the mevalonate pathway.\[8\] Through a series of enzymatic reactions, mevalonate is converted into cholesterol, a crucial component of cell membranes and a precursor for steroid hormones, bile acids, and vitamin D.\[9\] Vitamin D metabolism primarily regulates calcium and phosphorus levels, crucial for bone health.\[10\] The synthesis of vitamin D begins in the skin, where 7-dehydrocholesterol (7-DHC) undergoes a series of enzymatic reactions, primarily in the liver, to yield cholesterol, a vital component of cell membranes and precursor for various bioactive molecules.\[15\] In contrast, 7-DHC serves as the substrate for vitamin D synthesis. Upon exposure to ultraviolet B (UVB) radiation, 7-DHC in the skin undergoes photolytic cleavage to form previtamin D3 (cholecalciferol). This vitamin D3 is then carried to the liver, where it undergoes hydroxylation by 25-hydroxylase enzyme to produce 25(OH) D3, also called calcidiol.\[12\] Finally, calcidiol undergoes further hydroxylation in the kidneys by the enzyme 1α-hydroxylase to form the biologically active form of vitamin D, 1, 25-dihydroxyvitamin D3 \[1, 25(OH) 2D3\], also known as calcitriol. Calcitriol regulates calcium and phosphorus absorption in the intestines and plays crucial roles in bone mineralization, immune function, and cellular growth and differentiation.\[12-13\] Both cholesterol synthesis and vitamin D metabolism are tightly regulated processes that contribute to overall health and homeostasis in the human body. Their interconnectedness underscores the importance of understanding their roles and regulation in health and disease.\[14\]

**Fig. 1: Synthesis of vitamin D (conversion of UVB conversion to 7-dehydrocholesterol)**

**Biosynthetic Pathways**

**Common precursor molecules and intermediates**

The interplay between cholesterol synthesis and vitamin D metabolism is characterized by shared biosynthetic pathways and common precursor molecules, notably 7-dehydrocholesterol (7-DHC).\[14\] Within the cholesterol synthesis pathway, 7-DHC undergoes a series of enzymatic reactions, primarily in the liver, to yield cholesterol, a vital component of cell membranes and precursor for various bioactive molecules.\[15\] In contrast, 7-DHC serves as the substrate for vitamin D synthesis. Upon exposure to ultraviolet B (UVB) radiation, 7-DHC in the skin undergoes photolytic cleavage to form previtamin D3, which subsequently undergoes thermal isomerization to produce vitamin D3 (cholecalciferol).\[16\] Further hydroxylation steps in the liver and kidneys yield the biologically active form of vitamin D, calcitriol.\[17\] The utilization of 7-DHC as a precursor in both pathways underscores
their biochemical interconnectedness.\[18\] This shared precursor molecule highlights the potential for regulatory crosstalk between cholesterol synthesis and vitamin D metabolism, emphasizing the complexity of their interplay and its implications for physiological processes and disease states.\[2\].

**Enzymes responsible for cholesterol synthesis**

**HMG-CoA Synthesis**

In cholesterol biosynthesis, cytoplasmic HMG-CoA is formed from acetoacetoy-CoA and a third acetyl-CoA molecule, catalyzed by acetyl-CoA acetyltransferase 2 (ACAT2) and cytosolic HMG-CoA synthase (encoded by HMGCS1).\[19\] ACAT2 facilitates the condensation of two acetyl-CoA units to produce acetoacetyl-CoA. Subsequently, HMGCS1 converts acetoacetyl-CoA and an additional acetyl-CoA into HMG-CoA.\[20\] This cytoplasmic pathway mirrors the mitochondrial process, albeit with distinct enzymes. The HMGCS1 gene, located on chromosome 5p12, produces various isoforms via alternative splicing, contributing to the regulation of cholesterol synthesis.\[21\]

**Isopentenyl pyrophosphate (IPP) Synthesis**

The conversion of mevalonate 5-diphosphate to isopentenyl pyrophosphate (IPP) involves an ATP-dependent decarboxylation, yielding an activated isoprenoid molecule. This synthesis is catalyzed by diphosphomevalonate decarboxylase, also known as mevalonate-5-pyrophosphate decarboxylase, encoded by the MVD gene located on chromosome 16q24.2.\[22\] The MVD gene comprises 13 exons encoding a 400 amino acid protein. IPP interconverts with DMAPP via isopentenyl-diphosphate delta isomerase, also known as isopentenyl pyrophosphate isomerase.\[23\] Humans possess two isopentenyl-diphosphate delta isomerase genes, IDI1 and IDI2. The IDI1 gene, located on chromosome 10p15.3. IDH2 gene, found on chromosome 10p15.3, consists of 8 exons, giving rise to four differently spliced mRNAs, which produce three protein isoforms. These proteins are found within peroxisomes. Similarly, the IDI2 gene, also situated on chromosome 10p15.3, has 5 exons and codes for a 227-amino acid protein.\[24\]

**Squalene synthesis**

The synthesis of geranyl pyrophosphate (GPP) involves the combination of one molecule of IPP with one molecule of DMAPP, catalyzed by farnesyl diphosphate synthase, encoded by the FDPS gene. This gene, found on chromosome 1q22, produces three isoforms through alternative splicing. Squalene, critical in cholesterol synthesis, is produced by farnesyl-diphosphate farnesyltransferase 1, or squalene synthase, encoded by the FDFT1 gene on chromosome 8p23.1. FDFT1 generates five isoforms via alternative splicing from its 14-exon structure.\[25-26\] The FDFT1 gene consists of 14 exons, leading to the generation of 11 alternatively spliced mRNAs. These various transcripts collectively produce five isoforms of farnesyl-diphosphate farnesyl transferase 1.\[27\]

**Squalene to Lanosterol**

The recognizable steroid ring system originated with lanosterol. It first appears when the double bond in squalene, which is produced from DMAPP by farnesyl pyrophosphate, is epoxidized. Squalene epoxide then goes through cyclization. NADPH (Fig 3) is used by the enzyme that catalyses the production of epoxides to lower molecular oxygen and produce epoxide.\[27\]

**Lanosterol to 7-Dehydrocholesterol**

Lanosterol's destiny depends on the cell's requirements and the need for various steroids. It
can follow two pathways: the Bloch pathway, ending with desmosterol synthesis, convertible to cholesterol by 24-dehydrocholesterol reductase, encoded by DHCR24. The Kandutsch-Russell pathway, predominant in humans, converts lanosterol into 7-dehydrocholesterol (Fig 4).\[28\]

**Clinical Relevance in Disease States**

**Tuberculosis**

The prevalence of the global spread of tuberculosis (TB), the prolonged period of therapy, the low accessibility of tuberculosis treatment medications, and the rise in infections caused by drugs resistant to first-line treatment (MT), it is imperative to further investigate for novel medications or dietary supplements that may shorten the duration of therapy and improve the efficacy of currently available medications.\[29-30\] The major role of active vitamin D against MT has been confirmed in vitro by various studies, but the argument is still unresolved because randomised controlled trials (RCTs) was against objectives and the in vivo study results are unclear. In an in vivo investigation using mice, Jing Zhang et al., examined the therapeutic combination of pyrazinamide (PZA) and vitamin D. According to this study, using PZA and calcitriol combined prevents bacterial growth and causes the healing of lung lesions caused by MT. Furthermore, vitamin D administration in conjunction with (Fig 5) PZA medication increases the release of antimicrobial compounds such as LL-37 and anti-inflammatory cytokines such as IL-4. In individuals on PZA therapy, the levels of these compounds would fall in the absence of vitamin D supplementation.\[31\]
Significant advantages on sputum conversion have not been demonstrated in spite of numerous studies on vitamin D supplementation. This has been shown due to the trials were insignificant and had insufficient data. To evidently determine that vitamin D supplementation is effective in treating tuberculosis, more clinical trials are required.[32]

**Musculoskeletal Consequences of Vitamin D Deficiency**

The body's ability to maintain calcium equilibrium depends critically on vitamin D. After being produced in the skin or taken in through diet, it undergoes metabolic changes to become active. Low levels of vitamin D in the bloodstream are common and can reduce calcium absorption, leading to decreased levels of ionized calcium.[33] This prompts the release of parathyroid hormone, which can cause bone loss over time. Vitamin D deficiency is typically defined as having low levels of a specific form of vitamin D in the blood. Recent research suggests that combining vitamin D with calcium can help prevent fractures in older adults, especially when adherence to treatment is high and vitamin D doses are adequate.[34-35] Besides its role in calcium balance, vitamin D may also impact cell function and the immune system.[36] The most recent data from observational research, randomised controlled trials, and biochemical tests (RCTs) indicates that maintaining serum 25(OH)D levels at least 20 ng/mL is vital for normalizing PTH levels, reducing the risk of osteomalacia, and optimizing bone and muscle function.[37, 38] Many experts suggest 30 ng/mL as the threshold for optimal bone health.[39] Insufficient 25(OH) D levels lead to secondary hyperparathyroidism, increased bone turnover, bone loss, and heightened fracture risk. Rickets, primarily caused by vitamin D deficiency, presents with clinical signs like rachitic rosary, widened epiphyseal plates, and bowing deformities in children.[40] In adults, maintaining 25(OH)D levels beyond the threshold where PTH is normalized may not confer additional bone benefits. Adequate vitamin D supplementation, typically 800 to 1000 IU daily, enhances muscle strength and balance, with calcium intake being crucial for optimal outcomes.[41-42] However, factors such as age and calcium supplementation may influence the efficacy of vitamin D supplementation on muscle performance.[43] According to the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), current recommendations emphasize the importance of maintaining serum 25(OH)D levels above 20 ng/mL for optimal bone health in elderly and postmenopausal women.[44-45]

**Osteoporosis and Osteopenia**

Vitamin D deficiency is intricately linked to the development and progression of osteoporosis and osteopenia two conditions indicated by a reduction in bone density and an elevated risk of fractures.[46] Vitamin D plays a pivotal role in calcium absorption from the intestines, bone mineralization, regulation of parathyroid hormone secretion, muscle function, and immune modulation. Insufficient vitamin D levels lead to impaired calcium absorption, increased bone resorption, weakened bones, and compromised muscle function, all of which contribute to the pathogenesis of osteoporosis and osteopenia. Addressing vitamin D deficiency through supplementation, dietary adjustments, and lifestyle modifications is crucial in the management and prevention of these bone disorders, alongside regular monitoring of vitamin D levels and bone density to optimize bone health and reduce fracture risk.[45, 47]

Tanzy, Margaret E et al., This study supports the use of Bone Turnover Markers (BTMs) in conjunction with repeated DXA scans to treat individuals who are losing bone. The results we obtained show that treating vitamin D deficiency efficiently lowers bone breakdown, even though an ideal threshold for Bone Specific Alkaline Phosphatase (BSAP) suppression is still unknown. It's yet unclear if the decrease in BSAP in both research groups turns into a reduction in fracture risk comparable to that which bisphosphonate demonstrated. Delaying bisphosphonate therapy until the vitamin D status is rectified appears to be a feasible option, nevertheless. In order to reduce fracture risk as quickly as possible for those with modest vit.D deficiency who also have a elevated risk of fractures, it is recommended to start pharmaceutical intervention as soon as the deficiency is overcome.[48]
Cardiovascular disease

Tappia, Paramjit S., et al. deficiency of vitamin D has been associated with the etiology and progression of heart failure, its precise role in human heart failure remains uncertain. Epidemiological evidence, supported by experimental studies showing that mice lacking the vitamin D receptor (VDR) develop myocardial hypertrophy and dysfunction, suggests a potential link. However, there is considerable inconsistency between the findings of experimental studies and clinical intervention trials. Consequently, further research is necessary to determine whether adjunctive vitamin D supplementation therapy plays a role in managing patients with chronic heart failure. Recent clinical intervention studies have failed to establish a causal relationship between vitamin D supplementation and cardioprotection.

Health Implications and Clinical Considerations

Vitamin D deficiency and Cardiovascular Health

Disruptions in the interplay between cholesterol synthesis and vitamin D can lead to deficiencies in the latter, potentially impacting cardiovascular health. Vitamin D deficiency has been linked to increased risk factors for cardiovascular diseases such as hypertension, atherosclerosis, and coronary artery disease. Understanding the relationship between cholesterol and vitamin D levels is crucial for assessing cardiovascular risk and implementing appropriate interventions.

Bone Health and Osteoporosis Risk

The health of bones and the absorption of calcium depend on vitamin D. Inadequate vitamin D levels, influenced by cholesterol metabolism, can contribute to reduced bone mineral density and increased risk of fractures, particularly in elderly populations. Clinicians must consider both cholesterol and vitamin D status when evaluating osteoporosis risk and developing management strategies.

Immune Function and Inflammatory Disorders

Immunomodulatory effects of vitamin D impact both innate and adaptive immune responses. Deficiencies in Vitamin D, influenced by cholesterol levels, have been implicated in various inflammatory disorders, autoimmune diseases, and susceptibility to infections. Recognizing the intricate relationship between cholesterol synthesis and vitamin D is essential for managing immune-related conditions and optimizing immune function.

Metabolic Syndrome and Diabetes

Dysregulation of cholesterol metabolism and vitamin D levels may contribute to the development of metabolic syndrome and type 2 diabetes. Vitamin D deficiency has been associated with insulin resistance, dyslipidemia, and obesity, components of metabolic syndrome. Clinicians should consider assessing both cholesterol and vitamin D status in individuals with metabolic risk factors to mitigate the progression of these conditions.

Clinical Assessment and Management Strategies

Integrating measurements of cholesterol and vitamin D levels into routine clinical assessments enables a comprehensive evaluation of metabolic and cardiovascular health. Tailored management strategies, including lifestyle modifications, supplementation, and medication adjustments, can help optimize cholesterol and vitamin D levels, thereby decreasing risk of associated health complications.

CONCLUSION

In conclusion, the intricate exploration of cholesterol synthesis, vitamin D metabolism, and their associated enzymes provides invaluable insights into human health and disease. Delving into the complex pathways underlying cholesterol synthesis and vitamin D metabolism illuminates critical clinical implications, ranging from the roles of specific enzymes in cholesterol synthesis to their relevance in conditions like dyslipidemia and osteoporosis. This understanding informs targeted therapeutic interventions, emphasizing the importance of maintaining a delicate balance for overall well-being. Moving forward, future research directions in these areas hold promise for advancing clinical knowledge and enhancing patient care through the identification of novel therapeutic targets and personalized treatment approaches tailored to individual patient profiles. Additionally, further exploration of the interplay between
cholesterol and vitamin D in emerging disease states offers opportunities for preventive and therapeutic interventions, ultimately improving overall health outcomes.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest.

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