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Review

Beyond deficiency; bidirectional metabolic dysregulation between adipose tissue inflammation and vitamin D bioavailability in pediatric obesity

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Abstract

Pediatric obesity is characterized by a bidirectional metabolic dysregulation of vitamin D metabolism within adipose tissue, creating a state of functional deficiency that standard serum measurements often underestimate. Expanded adipose mass acts as a volumetric sink, sequestering fat-soluble vitamin D metabolites and contributing to low circulating 25-hydroxyvitamin D levels, inversely correlated with body fat. Crucially, adipose tissue inflammation drives profound local metabolic disruption, where pro-inflammatory cytokines (TNF-α, IL-6) down-regulate the activating enzyme CYP27B1 (1α-hydroxylase) and upregulate the degrading enzyme CYP24A1 (24-hydroxylase) in adipocytes and macrophages. This 'double hit' severely diminishes 1,25-dihydroxyvitamin D [1,25(OH)2D] within the adipose microenvironment, impairing vitamin D receptor (VDR) signaling precisely where it is needed to suppress inflammation. Systemic inflammation further compromises vitamin D status by reducing hepatic CYP2R1 activity, limiting the conversion of vitamin D to 25(OH)D. Additionally, obesity-associated alterations in vitamin D-binding protein (DBP) levels and isoforms may reduce the bioavailable (free) fraction of vitamin D metabolites, exacerbating tissue-level deficiency despite potentially borderline total serum 25(OH)D. Consequently, the combination of sequestration, inflammation-induced dysregulation of activating/degrading enzymes, and altered binding protein dynamics creates a significant disconnect, where standard serum 25(OH)D levels fail to reflect the critical local deficiency of bioactive vitamin D within the inflamed adipose tissue of obese children. This tissue-specific functional deficiency, driven by inflammation, underpins the impaired immunomodulation and perpetuates metabolic dysfunction, highlighting the inadequacy of conventional vitamin D assessment in obesity and necessitating consideration of bioavailability and tissue metabolism.

Keywords: Vitamin D, Adipose tissue, Pediatric obesity, Inflammation, Parathyroid hormone

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Introduction

Obesity and vitamin D deficiency are both established as global epidemics, sharing common risk factors such as poor diet and physical inactivity; since, recent focus is around the complex and bidirectional metabolic dysregulation involving adipose tissue inflammation and vitamin D bioavailability in the context of pediatric obesity (1). Recent observational and clinical studies consistently demonstrate an inverse correlation between vitamin D status and fat mass (2). However, the precise nature of this relationship, whether vitamin D deficiency attributes to obesity or is a consequence of it, and the regulatory interactions between excess adiposity and vitamin D activity remains an area of active investigation (3). Obesity in children can lead to negative health outcomes, including insulin resistance, inflammation, and impaired bone mineralization, increasing the future risk of cardiovascular disease, osteoporosis and type 2 diabetes (1). White adipose tissue, far from being a mere energy reservoir, secretes various molecules known as adipokines, which regulate numerous metabolic pathways and functions under normal conditions (4). In the development of obesity, the physiology of adipose tissue becomes severely disrupted, leading to dysfunctions such as a low-grade inflammatory state (5). This condition results in a dysregulation of adipokine secretion, contributing to the failure of certain metabolic pathways and an insulin-resistant state, which may lead to type 2 diabetes (6). In addition, bidirectional crosstalk amid neutrophils and adipocytes further strengthens adipose

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Implication for health policy/practice/research/medical education

There is a clear bidirectional metabolic dysregulation between adipose tissue inflammation and vitamin D bioavailability in pediatric obesity. In addition, obesity can lead to vitamin D deficiency through mechanisms like sequestration in adipose tissue and altered metabolism, vitamin D itself plays an active role in adipose tissue biology, influencing adipogenesis, energy metabolism, and inflammatory responses. Though several studies show the anti-inflammatory potential of vitamin D, further large-scale; however, well-designed randomized controlled trials are still mandatory to fully illuminate the optimal vitamin D supplementation strategies and their impact on inflammatory markers and overall metabolic health in obese children.

tissue inflammation (7). Adipose tissue also serves as a crucial site for vitamin D storage and metabolism, influencing multiple aspects of its biology including adipogenesis, energy metabolism, and inflammation (8). Meanwhile, vitamin D deficiency is prevalent in pediatric obesity, with studies showing a higher incidence in obese children compared to normal-weight peers (9). A previous study found, of 273 obese children, 56.8% had vitamin D deficiency or insufficiency, which significantly was higher than in a control group (10). Another study in Tunisian children reported vitamin D deficiency in 94% of obese cases compared to 17% in non-overweight controls (9). This stark contrast illustrates the strong inverse relationship between adiposity and vitamin D status in pediatric populations. The poor vitamin D nutritional status in obese children tends to worsen with age. This narrative review focuses on bidirectional metabolic dysregulation (9); while, inflamed adipose tissue actively disrupts vitamin D metabolism and bioavailability, then vitamin D deficiency, in turn, exacerbates adipose tissue dysfunction and inflammation, creating a self-perpetuating cycle that accelerates metabolic deterioration in the developing child (11). Focus on this vicious loop is critical, as it moves the discourse beyond mere deficiency correction towards targeting the underlying dysregulation that may underpin the progression of obesity-related comorbidities like insulin resistance, dyslipidemia, non-alcoholic fatty liver disease, and early cardiovascular risk markers in youth (11). This narrative review sought to consider the bidirectional metabolic dysregulation between adipose tissue inflammation and vitamin D bioavailability in pediatric obesity.

Method of the search

To identify relevant literature for this narrative review, we queried multiple databases including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar, using relevant keywords, such as 'vitamin D', 'adipose tissue', 'parathyroid hormone', 'pediatric obesity' and 'inflammation'.

A short look at the adipose tissue

Adipose tissue, particularly in its healthy state, is not merely a passive energy reservoir but also is a highly active endocrine organ secreting adipokines that regulate metabolism, appetite, and inflammation (12). In pediatric obesity, however, this tissue undergoes profound pathological remodeling (13). Hypertrophy of adipocytes outpaces the capacity for angiogenesis, leading to hypoxic regions within the expanding fat mass (14). Hypoxia acts as a potent trigger for endoplasmic reticulum stress and the activation of pro-inflammatory signaling pathways, notably the NF-κB (nuclear factor-kappa B) and c-Jun N-terminal kinase cascades (15). This results in a dramatic shift in adipokine secretion: anti-inflammatory adipokines like adiponectin are suppressed (16), while pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), monocyte chemoattractant protein-1 (MCP-1), and leptin (in its inflammatory role) are markedly upregulated (17). Concurrently, immune cell infiltration transforms the adipose tissue microenvironment. Resident macrophages shift from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 state, and there is significant recruitment of additional monocytes, T lymphocytes (particularly pro-inflammatory CD8+ and Th1 subsets), and even mast cells and neutrophils (18). This chronic, low-grade inflammation within adipose tissue is not confined locally; it spills over into the systemic circulation, contributing to insulin resistance in muscle and liver, endothelial dysfunction, and the systemic metabolic derangements characteristic of obesity (18).

Focus on the physiologic actions of vitamin D

Vitamin D, conversely, is a secosteroid hormone with pleiotropic effects extending far beyond classical calcium homeostasis (19). Its biologically active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], binds to the nuclear vitamin D receptor (VDR), which is expressed in nearly all human tissues, including adipocytes and immune cells within adipose tissue (19). Vitamin D signaling exerts potent immunomodulatory effects. It promotes a shift from a pro-inflammatory to an anti-inflammatory state by inhibiting NF-κB activation, reducing the production of TNF-α, IL-6, and IL-1β, and stimulating the secretion of anti-inflammatory cytokines like IL-10 (20). It also modulates macrophage polarization towards the M2 phenotype and regulates T-cell differentiation, suppressing Th1 and Th17 responses while promoting regulatory T-cell (Treg) function (21). Notably, VDR activation in adipocytes influences their metabolism, differentiation, and inflammatory profile (8). Vitamin D sufficiency appears to enhance insulin sensitivity within adipose tissue itself and may help regulate adipogenesis, potentially limiting pathological hypertrophy (22).

Mechanisms of vitamin D deficiency in obesity

Vitamin D deficiency observed in individuals with obesity is thought to result from reduced bioavailability, as the

vitamin becomes stored and retained within adipose tissue rather than being readily accessible for metabolic processes (23). Since vitamin D is fat-soluble, it is readily stored in adipose tissue, potentially reducing its circulating levels (8). Other contributing factors include reduced intestinal absorption, impaired metabolism, decreased liver 25(OH)D synthesis, a sedentary lifestyle leading to insufficient sun exposure, and inadequate dietary intake of vitamin D (24). It should remember that, adipose tissue is not only a storage site but also an important extra-skeletal target for vitamin D, meaning vitamin D can directly impact its function (25). The expression of both VDR and 25-hydroxyvitamin D 1α-hydroxylase (CYP27B1) genes has been observed in human adipocytes, suggesting that adipose tissue is capable of activating and inactivating vitamin D (26). Vitamin D may influence body fat mass by inhibiting adipogenic transcription factors and lipid accumulation during adipocyte differentiation. Furthermore, vitamin D metabolites appear to influence adipokine production and the inflammatory response within adipose tissue (8). Therefore, vitamin D deficiency may compromise the normal metabolic functioning of adipose tissue. The role of vitamin D in modulating adipose tissue inflammation is particularly relevant, when we know that obesity is characterized by a state of chronic low-grade inflammation (23). Inflammatory processes play a critical role in the onset of metabolic syndrome and various chronic diseases, with evidence suggesting that these pathophysiological changes may begin as early as childhood (9). The accumulation of excess adipose tissue induces profound alterations in metabolic activity, characterized by heightened release of pro-inflammatory mediators such as ILs (IL-6, IL-8, IL-1β, and IL-17), leptin, and TNF-α, accompanied by a reduction in the secretion of the anti-inflammatory adipokine adiponectin (27). These signaling molecules participate in intricate crosstalk between immune and metabolic pathways, contributing to the development of insulin resistance, elevated blood glucose, abnormal lipid profiles, and hypertension, which collectively heighten susceptibility to type 2 diabetes and atherosclerotic cardiovascular disease (28). Vitamin D receptors are widely expressed in immune and epithelial cells, enabling immune cells to synthesize calcitriol, through which vitamin D regulates immune cell differentiation, maturation, and metabolism while modulating cytokine production to exert anti-inflammatory and antioxidant effects (20). Clinical studies confirm that vitamin D status influences chronic inflammation in adipose tissue, and an inverse correlation between vitamin D status and serum C-reactive protein (CRP) levels has been observed (29). A recent study involving overweight and obese children noted lower baseline 25(OH)D levels and higher white blood cell (WBC) counts, granulocytes, monocytes, and CRP compared to normal-weight controls (30). After six months of vitamin D supplementation, a decrease in CRP levels was observed (30). While vitamin D supplementation appears to exert an anti-inflammatory effect primarily by reducing CRP levels and maintaining stable IL-10 values, its impact on pro-inflammatory factors like IL-17 and leukocyte profile parameters was not as significant in this study (30). Despite the anti-inflammatory properties of vitamin D and its potential to reduce pro-inflammatory mediators while increasing anti-inflammatory cytokines, the results regarding vitamin D3 supplementation on inflammatory markers in overweight and obese pediatrics and adolescents have been inconsistent (30). Six months of supplementation has been shown to significantly lower leptin concentrations and reduce the leptin-to-adiponectin (L/A) ratio, suggesting potential benefits for improving metabolic balance and reducing obesity-related risk factors (31). Leptin, recognized as both an anorexigenic hormone and a pro-inflammatory adipokine, promotes the upregulation of IL-6 and TNF-α, thereby attributing to the persistence of obesity-associated low-grade inflammation (16). In contrast, adiponectin functions as an adipokine with anti-inflammatory, anti-atherogenic, and insulin-sensitizing properties (32). The L/A ratio is considered a sensitive biomarker of early metabolic dysregulation in obese individuals (33). Furthermore, vitamin D deficiency increases the risk of insulin resistance through inflammation, adipokines, oxidative stress, and mitochondrial dysfunction, leading to metabolic disorders of glucose and lipid metabolism closely related to obesity and metabolic syndrome in children (34). The relationship between vitamin D and adipokines is further highlighted by negative correlations between vitamin D levels and leptin and resistin, and a positive association with adiponectin concentrations (35). The optimal vitamin D status in obese children and the effectiveness of vitamin D supplementation in mitigating circumstances associated with childhood obesity require more research (36). Current Endocrine Society guidelines suggest that obese individuals often require approximately two to three times higher doses of vitamin D supplementation than those with normal body weight to achieve comparable serum levels (37). Therapeutic regimens typically involve cholecalciferol at 3000–6000 IU/day for children aged 1 to 12 years and 6000 IU/day for adolescents, followed by maintenance doses of 600-1000 IU/kg/day (maximum 4000 IU/day) after repletion (38). However, dosing should be individualized based on baseline levels, clinical context, and serial monitoring of parathyroid hormone, 25(OH)D, calcium levels to avoid potential toxicity while ensuring therapeutic efficacy (39).

Clinical presentation of vitamin D deficiency in children

The clinical manifestations of this bidirectional dysregulation between adipose tissue inflammation and vitamin D deficiency are evident in pediatric cohorts (40). Obese children and adolescents consistently exhibit lower serum 25(OH)D levels compared to lean peers,

with the degree of deficiency often correlating with BMI z-scores, waist circumference, and markers of adiposity like visceral fat area measured by imaging (41). Crucially, low vitamin D status in these children is not merely an epiphenomenon; it is independently associated with worse metabolic profiles (42). Studies show that obese children with vitamin D deficiency have significantly higher levels of fasting insulin, HOMA-IR (a measure of insulin resistance), triglycerides, and inflammatory markers (like CRP, IL-6, TNF-α) compared to obese children who are vitamin D sufficient (43). They also show higher prevalence and severity of NAFLD, characterized by elevated liver enzymes (ALT, AST) and increased hepatic fat on ultrasound or MRI (44). The dysregulation extends to vascular health; since, vitamin D deficiency in obese youth correlates with endothelial dysfunction and higher blood pressure as the early markers of atherosclerosis (45). Importantly, these associations often persist after adjusting for BMI, suggesting vitamin D status has an independent modulatory role on metabolic and cardiovascular risk beyond the mechanical effects of excess weight (46). The complexity of this relationship is highlighted by intervention studies. While vitamin D supplementation in deficient obese children often successfully raises serum 25(OH)D levels, the metabolic benefits are frequently modest and inconsistent (36). Some studies report improvements in insulin sensitivity, reductions in inflammatory markers, or modest decreases in blood pressure, while others show minimal effects. This inconsistency strongly suggests that simply correcting the serum concentration of the precursor 25(OH)D does not automatically resolve the underlying tissue-level dysregulation (47). The inflamed adipose tissue environment, with its downregulated CYP27B1, upregulated CYP24A1, and altered D binding protein (DBP) dynamics, may prevent the supplemented vitamin D from being effectively converted to its active form where it is needed most or from reaching target cells in a bioavailable form (48). The duration of obesity and inflammation may also lead to irreversible changes in adipose tissue architecture and cellular composition, creating a less responsive tissue bed. This underscores that the problem is not merely a lack of substrate (vitamin D), but a fundamental dysregulation of its metabolism and action within the pathological adipose tissue microenvironment (3). Supplementation strategies may need to be more aggressive, longer in duration, or combined with interventions that directly target adipose tissue inflammation (e.g., weight loss, specific anti-inflammatory agents) to overcome this barrier (49).

Conclusion

The bidirectional association between obesity and vitamin D status represents a complex interplay of multiple mechanisms. While adipose tissue expansion creates a volumetric sink that sequesters vitamin D metabolites, the inflammatory microenvironment of obese adipose tissue actively disrupts vitamin D metabolism through cytokine-mediated suppression of activating enzymes and induction of degrading enzymes. Compounding these effects, alterations in vitamin D binding protein expression and polymorphisms in obesity may further reduce the bioavailable fraction of vitamin D metabolites. Together, these mechanisms—sequestration, enzymatic dysregulation, and altered binding protein dynamics—create a tissue-specific functional deficiency that cannot be adequately assessed by standard serum 25(OH)D measurements alone. Breaking this cycle likely requires integrated approaches combining weight management strategies with targeted vitamin D repletion protocols specifically designed for the obese pediatric population.

Authors' contribution

Conceptualization: Abbas Boskabadi and Seyed Hossein Saadat.
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Writing—original draft: All authors.
Writing—review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity and Grammarly to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

Ethical issues

The authors have completely observed ethical issues (including plagiarism, data fabrication, and double publication).

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