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NARRATIVE REVIEW

Dissecting pathways of cancer-associated cachexia and its evidence-based relation to vitamin D

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Abstract

Introduction: Cancer-associated cachexia (CAC) is a complex metabolic syndrome. It affects 0,5-1% of the general population and 60-83% of cancer patients. Vitamin D has a potential immunological role in cancer cachexia. However, the mechanism remains unclear.

Method: This review outlines the complex mechanisms of CAC, a metabolic syndrome marked by muscle loss affecting 80% of cancer patients and the potential action of vitamin D. We highlight the limited studies exploring vitamin D's impact on CAC, based on cachexia parameters.

Result: The Warburg effects in CAC are understood to involve elevated energy use, driven by the tumor microenvironment (TME) and pro-inflammatory cytokines. This present review explores the mechanism of cachexia on skeletal, adipose tissue, liver and tumor microenvironment. At the same time vitamin D deficiency in cancer correlates with poor prognosis due to its critical role in immune modulation. Notably, various clinical trials showed the beneficial roles of vitamin D in reducing inflammation, pain and increasing weight.

Conclusion: Few studies had explored the beneficial effects of vitamin D in cancer; However, limited evidence exists on immunomodulatory effects of vitamin D. This critical gaps stressing the need for further clinical research across various cancer types.

Keywords: cancer-associated cachexia, vitamin D

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Introduction

Cachexia is a complex metabolic syndrome marked by muscle loss, often with fat loss, partially reversible with nutritional support.[1,2] It affects 0,5-1% of the general population and 60-83% of cancer patients.[1] It causes 20% of cancer deaths, often when weight loss exceeds 30-40%.[3] Diagnosis can use cachexia score (CASCO) or miniCASCO, or simplified criteria: > 5% weight loss in 6 months, or ≥ 2% with BMI < 20 kg/m^2 or sarcopenia.[1,4,5] Pre-cachexia and refractory cachexia also exist. About 60% of patients in hospital in their 70s face sarcopenia, frailty, cachexia, or malnutrition, worsening outcomes.[6] Cachexia affects 40-60% of older male and 40-50% of older female cancer patients.[7]

Low serum of 25-OH vitamin D is common in prostate, breast, ovarian, and colorectal cancers,[9] and it is linked to cancer risk and outcomes.[10] Vitamin D and its analogues may reduce metastasis and mortality.[11] However, European Society of Parenteral and Enteral Nutrition (ESPEN) states vitamin D does not prevent muscle loss in cancer.[11] Still, it has a potential anti-inflammatory effects, and immunological role by reducing T-cell and B-cell activity and cytokines (IFN-γ, IL-6, IL-2, TNF-α), key in cachexia development.[12] However, the underlying mechanism by which vitamin D influences cachexia and its interaction in cancer progression remains unclear, representing critical gap in current knowledge in cancer cachexia.

Cancer-associated cachexia

Cancer-associated cachexia is a complex interplay of metabolic dysregulation, characterized by systemic inflammation due to tumor-related factors. On clinical presentations, the patients appear cachetic with involuntary weight loss. The tumour energy demands range from 100–1400 kcal/day.[13] Cachexia risk varies by tumor type.[14] It involves a negative energy balance driven by the Warburg and reverse Warburg effects.[15,16] In the Warburg effect, tumor cells use inefficient aerobic glycolysis, leading to high glucose uptake and lactate production that acidifies the tumor microenvironment (TME), promoting immune evasion.[15,17] The Cori cycle adds to energy inefficiency by recycling lactate to glucose in the liver.[15] In the reverse Warburg effect, cancer-associated fibroblasts (CAFs) undergo glycolysis due to ROS and IL-6 exposure, releasing metabolites (lactate, pyruvate, ketones, glutamine) into the TME to fuel cancer growth and support metastasis and immune suppression.[13,15]

Liver, muscle, and adipose tissue support this altered metabolism. The liver compensates early on but later contributes to muscle wasting and lipolysis via IL-6.[18] Elevated bile acids also worsen muscle loss via TGR5 receptor activation.[14] Muscle loss occurs through increased proteolysis (via ubiquitine-proteasome system (UPS), calcium-activated systems, autophagy-lysosome) and reduced protein synthesis, with TNF-α-activated NF-κB increasing MuRF-1 expression.[14,18] Reduced mammalian target of rapamycin (mTOR) activity triggers abnormal autophagy and mitophagy via AMPK–FOXO–mTORC1 disruption.[19] Early-stage cachexia also involves white adipose tissue (WAT) lipolysis, releasing fatty acids and converting WAT into thermogenic beige cells, worsening energy imbalance.[14,20]

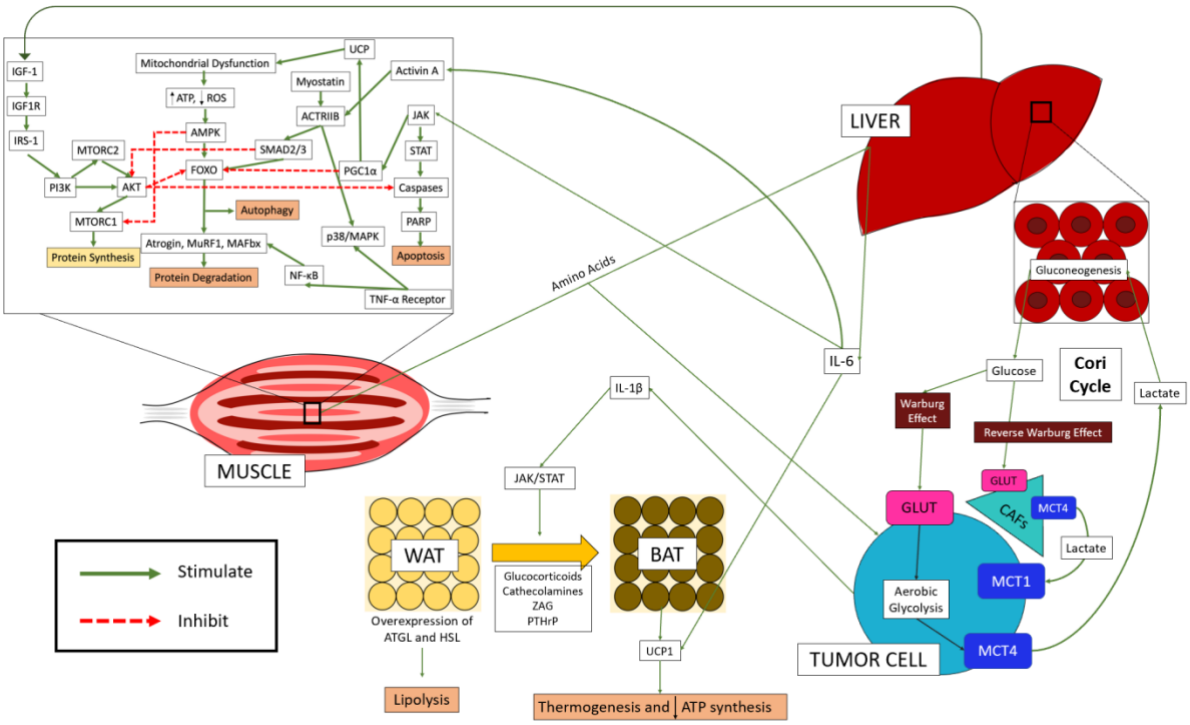

Figure 1. Mechanisms of cachexia in the skeletal muscle, adipose tissue, liver, and tumor microenvironment (TME). Tumor cells use glucose via the Warburg or reverse Warburg effect, producing lactate for energy. Interleukine-6 (IL-6) from the liver drives muscle wasting, thermogenesis, and reduced ATP via JAK/STAT and FGF/p38 MAPK pathways. In WAT, IL-6 and TNF-α induce lipolysis through ATGL and HSL, while adipocyte browning is promoted by glucocorticoids, catecholamines, ZAG, and PTHrP.

Note: GLUT1, glucose transporter 1; PEPCK, phosphoenolpyruvate carboxykinase; MCT4, monocarboxylate transporter 4; CAFs, cancer-associated fibroblasts; OXPHOS, oxidative phosphorylation; IL-6, interleukin-6; JAK, janus kinase; STAT, signal transducers and activators of transcription; FGF, fibroblast growth factor; MAPK, mitogen-activated protein kinase; UCP1, uncoupling protein 1; WAT, white adipose tissue; BAT, brown adipose tissue; ZAG, zinc-α2-glycoprotein; PTHrP, parathyroid-hormone-related protein. (Figure was modified from Archid R[13], Peixeto[14], Wang[18], and Bonaficio A[19]. This modification has not been published elsewhere).

Proteolysis and impaired protein synthesis in cardiac muscle resemble those in skeletal muscle.Insulin resistance, common in CAC, worsens muscle and fat loss by enhancing gluconeogenesis and disrupting PI3K/AKT/mTOR signaling; this often improves after tumor removal. In Drosophila, tumor secreted ImpL2 (an IGFBP analog) disrupts muscle metabolism.16,24 TNF-α also promotes insulin resistance by affecting insulin receptor signaling.[18]

The brain-gut axis regulates appetite and energy via neuropeptides (e.g., substance P, NPY, CGRP).[18] Hypothalamic pathway involving POMC, IL-6, leptin, ghrelin, GDF15, and others influence thermogenesis and lipolysis through neurons like AgRP and PVH.[18,21] Additional regulators include GLP-1, LCN2, and INSL3, which affect appetite via MC4R signaling.[21,22] Tumor derived factors like TNF-α, neutrophils, and sphingosine 1-phosphate can cross the blood-brain barrier, promoting anorexia. Macrophage inhibitory cytokine-1 (MIC-1) further suppresses appetite through TGF-β receptor interaction in the hypothalamus.[21]

Further involvement of cytokines and immune cells in the development of cachexia and cancer outcome

Pro-inflammatory mediators (TNF-α, IL-1, IL-6, IL-8, TGF-β, NF-κB) drive inflammation, anorexia, and muscle loss in CAC.[23,24] The special cluster of TNF superfamily, TWEAK (TNF-Related Weak Inducer of Apoptosis) induces atrophy via NF-κB.[23] Interleukin-1α (IL-1α) affects appetite, though IL-1β depletion did not ease fatigue.[21,23,25] Interleukin-2 (IL-2), IL-10, EGF, and IFN-γ activate JAK/STAT; IL-10 suppresses protein synthesis via mTOR, IL-6 promotes glycolysis, and IL-8 supports tumor growth.[14,26,27] Interferon-γ (IFN-γ), IL-20, Activin A worsen wasting, while IL-4 may be protective.[19,26,28] Tumor Growth Factor-β (TGF-β) and GDF-15 impair muscle via separate pathways.[23,26] Vitamin D promotes apoptosis via BAX/BCL-2 modulation, helping limit systemic damage in CAC.[29,30]

Tumor associated macrophages (TAMs) polarize to anti-tumor (M1) or pro-tumor (M2); high M2 or low M1/M2 ratio correlates with poor prognosis.[31,33] The CD47 and SIRPα+ macrophages are negative markers in sarcoma.[32] Interleukine-4 (IL-4) improves muscle and survival in colon cancer.[33] High neutrophils (NLR > 3.15) predict cachexia and worse outcomes in several cancers.[34,35] In mice, glycolysis inhibition raised neutrophils and accelerated cachexia.[36] The CD4+ T-cells aid macrophages and improve outcomes; CD8+ T-cells may reduce cachexia when depleted.[36-38] Naive CD4+ CD44low cells may preserve muscle.[39] The B-cells, NK cells, MDSCs, and mast cells have unclear roles, though MDSCs and CAFs promote WAT browning, IL-6, TGF-β, and PTHrP release, and M2 polarization, worsening cachexia.[23]

Anti-inflammatory effect of vitamin D in cancer-associated cachexia patients

Vitamin D is a fat-soluble vitamin. Its main source of vitamin D is direct exposure to sunlight which provides ultraviolet B (UVB) photons wavelength 285-320 nm to allow the penetration in dermis and epidermis, which then undergoes metabolism and activation in liver and kidney. The classic function of vitamin D is to promote the intestinal absorption of calcium by mediating active calcium transport across the intestinal mucosa. If the levels of 25(OH) vitamin D are low, only a small fraction of dietary calcium is absorbed, which leads to increase bone turnover and reduces bone mineral density. Therefore, for the optimal musculoskeletal and bone health, the levels of 25(OH) vitamin D should be at least 30 ng/ml.[40]

Beyond its well-known role in bone, vitamin D also serves in numerous extraskeletal function. Vitamin D, particularly $1,25(OH)_2D_3$, modulates innate immunity by stimulating defensin β2 and CAMP in monocytes and macrophages, enhancing chemotaxis, autophagy, and IL-15 secretion.[12,27] It also affects keratinocytes and various epithelial cells. Vitamin D receptor (VDR) is expressed in T cells, B cells, and macrophages. Vitamin D inhibits dendritic cell maturation and B-cell activity, promotes Th2 (via IL-4, IL-5, IL-10), and suppresses Th1 cytokines (e.g., IL-12, IFN-γ, TNF-α).[12] It also reduces Th17 through Foxp3+ Treg induction and IL-10 production. However, human studies vary due to differences in vitamin D levels and analogues used.

Vitamin D deficiency correlates with cancer and poor prognosis. Its anticancer roles include anti-inflammation, autophagy, apoptosis, antiproliferation, and differentiation.[27,41] It modulates TME via IL-10 upregulation, IL-6/IL-8 inhibition, TGF-β suppression, MKP5 promotion, NF-κB inhibition, and reduced prostaglandin and COX-

2/PGE2 pathways. The COX-2 suppression limits VEGF-driven angiogenesis.[27] Calcitriol plus progesterone reduces CXCL1/2 and proteins linked to metastasis and survival.[42] It also reduces DC activation markers (CD40, CD80, CD86), decreases IL-12, and increases IL-10, lowering T-cell activation.[27]

Despite these roles, studies linking vitamin D and cachexia remain scarce. A PubMed search (November 2022-2023) using 'cachexia' and CASCO parameters revealed inconsistent results **(Table 1).**

Table 1. Evidence of vitamin D and individual aspects of cachexia according to CASCO.

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
In-vitro study	Sustova H, et al (2019)[43]	Mimic cancer (Lewis lung carcinoma)	co treatment with 25 Vit D or 1,25 Vit D in C2C12 myotubes induced muscle wasting by administering combination of TNF-α , IFN-γ or IL-6	25 Vit D prevented the reduction in myotubes diameter through activation of Akt signaling. However, 1,25 (OH)2 D showed had no protective effect on myotubes as it was associated with an increased Fox03 expression.
Animal study	Camperi A et al.[44]	Rats induced hepatoma	10 nM concentration of 1,25 (OH)2 D	Administration of 1,25 (OH)2 D to mice bearing tumor does not modify the kinetic of cachexia appearance, in terms of both muscle wasting and adipose tissue depletion, whereas it further increases muscle VDR expression. There is lack of a direct link between cachexia and circulating Vit D levels
Clinical trial	Van Veldhuizen et al. (2000)[45]	Metastatic prostate cancer	Vitamin D 2000 IU/day for 12 weeks	Improvement of pain (25%) and muscle strength (37%)
	Hoffer et al. (2016)[46]	Advanced lung cancer	Consumption of 20,000 IU vitamin D daily with the largest meal of the day for 14 days followed by 10,000 IU per day for a further 7 days.	C-reactive protein (CRP) levels at baseline, 14 days (280,000 IU), and 21 days (350,000 IU) are 20.9 ± 36.8 mg/L, 17.0 ± 22.1 mg/L, and 16.7 ± 22.0 mg/L respectively, which showed a decreasing trend but not statistically significant.
	Haidari et al. (2020)[47]	Stage II or III colorectal cancer	Randomization to 4 groups of treatments for 8 weeks : Control group received a vitamin D placebo weekly + 2 omega-3 fatty acid placebo capsules daily Omega-3 fatty acid group received 2 omega-3 fatty acid capsules (each	No significant differences were observed in weight, BMI, and FFM% among four groups at baseline and after intervention. However, mean changes in these parameters were significantly different post-intervention ($p < 0.01$), with notable improvements in the three intervention groups compared to control ($p < 0.01$ for all). Within-group analysis showed that intervention groups

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			capsule containing 330 mg of omega-3 fatty acids) daily + a vitamin D placebo weekly Vitamin D group received a 50,000 IU vitamin D soft gel weekly + 2 omega-3 fatty acid placebo capsules daily Cosupplementation group received a 50,000 IU vitamin D soft gel weekly + 2 omega-3 fatty acids capsules (each capsule containing 330 mg of omega-3 fatty acids) daily.	experienced significant increases in weight, BMI, and percentage of fat-free mass, along with reductions in CRP, TNF-α, and IL-6, while the control group showed declined in those parameters. Serum IL-6, TNF-α, and CRP changes differed significantly among groups ($p < 0.001$), with the largest IL-6/CRP reduction in the vitamin D group, and greatest TNF-α reduction in the co-supplementation group. Pairwise comparisons confirmed significant drops in TNF-α and IL-6 in the vitamin D group ($p < 0.001$) and in all markers in the co-supplementation group ($p < 0.001$). The omega-3 group also showed significant reduction in TNF-α ($p = 0.01$) and CRP ($p = 0.04$) compared to control. Albumin levels significantly differed across groups at baseline ($p = 0.01$) and post intervention ($p < 0.01$). Within- group comparisons revealed significant albumin decreases in the control group ($p < 0.01$) and a smaller but significant decrease in the vitamin D group ($p = 0.02$).
	Peppone et al. (2018)[48]	41 females diagnosed with breast cancer (stage 0-III) within the previous five years.	The 4 treatment groups were: group 1 receiving high-dose weekly calcitriol (ChromaDex), group 2 performing individualized home-based progressive walking and resistance exercise program (EXCAP), group 3 receiving a combination of both treatments, and group 4/control group receiving a daily multivitamin (contained 400 IU of vitamin D and 200 mg of calcium) for 12 weeks	No significant difference between the four groups in BMI, VO_2max, handgrip, chest press, leg extension.
	Chandler et al. (2020)[10]	Invasive cancer (VITAL study)	Vitamin D3 (cholecalciferol, 2000 IU/d) and	Among Non-Hispanic White participants (163 vitamin D3, 205 placebo), vitamin D3

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			marine omega-3 fatty acids (1 g/d)	reduced cancer mortality (HR, 0.80; 95% CI, 0.65-0.98; P = 0.03). In patients with BMI < 25 kg/m^2, cancer mortality was lowest in the vitamin D group (HR 0.58 (0.39-0.86; p=0.007), with a significant interaction by BMI (p = 0.02). Similarly, total metastatic cancer and cancer mortality were lowest in the lower BMI group with vitamin D (HR 0.62 (0.45-0.86; p = 0.004), with BMI interaction p = 0.03).
	Brenner et al. (2021)[49]	Invasive cancer (VITAL study)	Vitamin D3 (cholecalciferol, 2000 IU/d) and marine omega-3 fatty acids (1 g/d)	Vitamin D3 supplementation was linked to a 14% significant reduction in advanced cancer risk (RR 0.86; 95% CI, 0.74-0.99). Among normal-weight participants, the risk of any and advanced cancer was lower but not statistically significant compared to obese participants (RR 0.86; 95% CI, 0.71-1.03 and RR 0.85; 95% CI, 0.59-1.2). The protective effect decreased with higher BMI, though not significantly.
Observational	Analan et al. (2020)[50]	Breast cancer	Division to lymphedema and control groups	Serum 25(OH)D3 levels did not show statistically significant differences between groups ($p > 0.05$). There was no correlation in the BCRL group between 25(OH)D3 levels and the VAS and Q-DASH scores or the diametric and volumetric differences of extremities ($r \leq 0.3$; $p > 0.05$).
	Dev et al. (2011)[51]	Advanced cancer patients	-	70% of fatigue and anorexic patients had vitamin D insufficiency (< 30 ng/mL) and 47% had 25(OH) vitamin D levels <20 ng/mL.
	Klement et al. (2021)[52]	Breast, rectal, and head and neck cancer patients.	-	Strongest correlation was an inverse correlation between vitamin D concentration and leucocyte count (Kendalls' $\tau = -0.173$, $p = 0.0065$), followed by an inverse correlation between vitamin D and CRP ($\tau = -0.172$, $p = 0.0071$)
	Castellano-Castillo et al. (2018)[53]	Colorectal cancer patients	Division into 2 groups; those who underwent colorectal surgery and control subjects who	Serum CRP levels were negatively correlated with serum 25(OH)D levels and positively correlated with both VDR

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			underwent hiatal hernia surgery or cholecystectomy	and NFκB1 gene expression in adipose tissue.
	Xie et al. (2017)[54]	Prostate cancer	-	An inverse association was found between serum 25(OH)D and prostate cancer (adjusted OR: 0.785; 95% CI: 0.718–0.858). In prostate cancer patients, serum 25(OH)D was negatively correlated with CRP ($r = -0.286$, $p < 0.05$) and IL-8 levels ($r = -0.376$, $p < 0.01$), while no such correlation was seen in controls.
	Skender et al. (2017)[55]	Colorectal cancer	-	Accelerometry-based vigorous and moderate-to-vigorous physical activity were positively associated with 25(OH)D3 levels ($p = 0.04$; $p = 0.006$).

VAS, visual analog scale; Q-DASH, Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire

CAC involves complex interactions between the tumor, systemic inflammation, and metabolic alteration. Vitamin D deficiency is considered a potential like factor or marker for CAC, particularly due to its association with muscle mass and strength loss. Vitamin D may also contribute to reducing pain, muscle wasting, anorexia, and pro-inflammatory responses. However, the direct therapeutic effect of vitamin D supplementation in reversing or preventing established CAC remains unclear, and current evidence is lacking to conclude its role in improving immune function for supporting therapy of cachexia.

Conclusion

Cachexia is complex and multi-factorial. It's not just a nutritional deficiency. This review hightlights critical gaps of understanding the effects of calcitriol ($1,25(OH)_2D_3$) and its role in immune function in CAC. However, limited evidence exists on immunomodulatory effects of vitamin D in cancer. It is emphasizing the need for robust clinical research across various cancer types to enhance cachexia outcome.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author's contribution

NRMM, A, IAP: Conceptualization, data acquisition, formal analysis, interpretation of results, drafting the manuscript, and final approval of the version to be published; A,FW,FN: Supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published; NRMM, IAP, FN: Conception and design of the study, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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