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Vitamin D should be considered as a targeted therapy in glioblastoma cases

Research Article

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Glioblastoma remains one of the most aggressive and malignant primary brain tumors, with treatment typically involving surgery, radiation therapy, and chemotherapy. More recently, novel approaches, such as immunotherapy and metabolomics, have emerged as promising adjuncts in the therapeutic landscape.

Metabolomics is an evolving field in medicine that investigates the interactions between metabolites and biological tissues. Unlike other omics fields, metabolomics provides a direct reflection of an individual's molecular phenotype. It enables the measurement of diverse metabolites that may serve as biomarkers for disease detection, prognosis, or even for guiding preventive strategies aimed at improving overall health status[1].

Among the critical metabolites in the human body is vitamin D and its active form, 1,25-dihydroxyvitamin D (1,25$(OH)_2D_3$ or calcitriol). The primary physiological roles of vitamin D include the regulation of calcium, magnesium, and phosphate homeostasis. However, additional functions, particularly within the central nervous system, have been recognized. For instance, calcitriol has been shown to enhance the activity of choline acetyltransferase, the enzyme responsible for catalyzing the biosynthesis of acetylcholine, a key neurotransmitter[2].

Another important function of vitamin D is the regulation of immunity[3]. This is primarily demonstrated through the stimulation of the innate immune system, as evidenced in patients with tuberculosis. The mechanism involves the enhanced antimicrobial activity of macrophages and monocytes, which is induced by the active metabolite of vitamin D. Specifically, vitamin D improves innate immune cell functions, such as chemotaxis and phagocytosis. Additionally, through binding to the retinoid X receptor, the vitamin D receptor (VDR) promotes the transcription of antimicrobial peptides.

Vitamin D also plays a significant role in adaptive immunity[3]. Studies have shown that upon activation of T and B lymphocytes, the expression of VDR and vitamin D-activating enzymes increases. Calcitriol, the active form of vitamin D, is believed to contribute to B-cell homeostasis and proliferation.

This metabolite is further involved in various T-cell functions, including endocrine signaling, the direct conversion of 25(OH)D to calcitriol, paracrine effects on T cells, and antigen presentation. A key regulator in this process is the vitamin D-binding protein, which inhibits the conversion of vitamin D to calcitriol in T cells. These immunological effects are mediated via the VDR and the enzyme CYP27B1, both of which are expressed in immune cells and in over 50 other tissue types[2]. Notably, vitamin D levels are often reduced in the bloodstream of patients with cancer primarily due to inflammation. Consequently, the immunoregulatory effects of vitamin D are considered to be dose-dependent[3].

According to current literature, vitamin D may play a significant role in cancer immunotherapy more broadly. Recent studies have shown that vitamin D can help mitigate the side effects of anti-cancer immunotherapies[4,5].

Regarding its role in glioblastoma therapy, the available data remain limited. Yuan et al.[6] demonstrated that vitamin D influences glial cell proliferation, thereby disrupting cholesterol homeostasis and development. Sze-Ching Lo et al.[7] reported that glioblastoma cells treated with vitamin D exhibited reduced invasiveness

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and migration. Morelli et al.[8] found that vitamin D decreased tumor cell proliferation on its own and enhanced the anti-proliferative effect of temozolomide (TMZ) when used in combination, without affecting normal cells. Notably, vitamin D combined with TMZ showed a synergistic antitumor effect *in vitro*. Clinically, treatment with calcitriol in glioblastoma patients has been associated with long-term remission and improved overall survival. Moreover, patients with serum vitamin D levels below 30 ng/mL had significantly poorer overall survival and progression-free survival than those with higher levels[9].

Notably, the expression of VDR is elevated in glioblastoma tissues compared to other glial tumors[10], and higher VDR expression is positively correlated with improved overall survival. A recent study by Elmaci et al.[11] further supported the therapeutic potential of combining vitamin D, all-trans retinoic acid, and TMZ in the management of glial tumors.

While vitamin D is widely recognized for its beneficial effects on bone health, immunity, and chronic disease prevention, excessive levels or inappropriate supplementation can lead to adverse outcomes. One of the most well-documented risks is vitamin D toxicity, or hypervitaminosis D, which results in hypercalcemia, causing symptoms, such as nausea, vomiting, muscle weakness, confusion, and in severe cases, kidney damage or failure[12, 13]. Additionally, excessive vitamin D intake may increase the risk of falls and fractures in the elderly, particularly when taken in high bolus doses, as shown in several randomized trials[14, 15]. Moreover, there is growing concern that very high levels of vitamin D may paradoxically suppress immune function, leading to increased susceptibility to infections or autoimmune imbalance. Furthermore, a U-shaped relationship has been observed between vitamin D levels and several health outcomes, suggesting that both deficiency and excess may be harmful[16]. These findings highlight the importance of monitoring serum vitamin D levels and personalizing supplementation to avoid potential toxicity or unintended immunomodulatory effects.

Despite the continuously expanding field of neuro-oncology, no studies to date have specifically examined the combined use of immunotherapy and vitamin D in glioblastoma treatment. Therefore, the authors suggest that it is time to shed light on this important issue, as the use of vitamin D has been already proven to be beneficial for patients with cancer, including those with glioblastoma, and to examine its role as a targeted therapy in the immunotherapy battle against glioblastoma. Although comprehensive metabolomic profiling in hospitals may be costly, a single vitamin D test is relatively inexpensive and could offer meaningful benefits for patients with cancer.

Conflict of interest

The authors declare that there is no conflict of interest.

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