Vitamin D: A complementary nutritional therapy for treatment of glioblastoma?

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Conflict of interest statement: None declared.

Provenance and peer review: Submitted and externally reviewed

Date first submitted: 10/11/2021
Date submitted after peer review: 14/4/2022
Acceptance date: 14/4/2022
Published online: 26/5/2022

To cite: Griffin S, Griffin F. "Vitamin D: A Complementary Nutritional Therapy for Treatment of Glioblastoma?" Adv Clin Neurosci Rehabil 2022;21(3):18-20
https://doi.org/10.47795/KYMF8006

Abstract

The active vitamin D hormone, 1,25-dihydroxyvitamin D_3, is well established to inhibit cellular proliferation and induce differentiation in several cell types of the central nervous system. Indeed, a myriad of studies demonstrate the important role 1,25-dihydroxyvitamin D_3 plays in maintaining a healthy brain and nervous system. This mini review will briefly summarise in vitro, in vivo, and epidemiological evidence related to the anti-proliferative and anti-cancer activities of vitamin D in hyperproliferative disorders like brain cancer. Here, we focus on the clinical application of 1,25-dihydroxyvitamin D_3 and vitamin D analogues (synthetic vitamin D-like compounds) in glioblastoma treatment and discuss their potential as efficacious and tolerable adjunct therapeutic agents for patients diagnosed with this aggressive form of brain tumour.

Glioblastoma accounts for approximately 50% of all brain tumours in adults and is considered incurable due to its heterogeneity and complex pathogenesis [1]. Despite advancement of modern therapies against glioblastoma, it remains a deadly disease with poor prognosis and significantly impacts on quality of life throughout the disease course [2]. Median patient survival rates range between 14-16 months following diagnosis, and a five-year survival rate of 9.8% in patients [1], resulting in a critical public health issue. Indeed, treatment of glioblastoma remains the most challenging task in clinical oncology. Current therapeutic management involves maximal surgical resection of the tumour along with radiation and concomitant adjuvant temozolomide (TMZ) therapy [3]. However, glioblastoma has a poor response to current conventional chemotherapeutics due to varying side effects along with a relatively short half-life of TMZ-based chemotherapy (1.8 hours) [1]. 1,25-Dihydroxyvitamin D_3 has emerged as a target of interest to be co-administered with different brain cancer treatments due its anti-proliferative and pro-differentiation effects in the CNS, including gliomas, and ability to cross the blood-brain-barrier [4-6]. Indeed, early studies conducted on rat glioma demonstrated that such cells respond to 1,25-dihydroxyvitamin D_3 [7]. Thus, there are long-standing academic and patient-specific interests in vitamin D supplementation as a possible concomitant therapy to counteract tumour growth or reduce cancer risk.

Vitamin D and Vitamin D Analogues: Regulators of cell proliferation

Multiple in vitro studies have shown that 1,25-dihydroxyvitamin D_3 promotes a proliferation-to-differentiation switch in several cell types by promoting progression through the cell cycle and subsequently driving the cells to a more differentiated phenotype [5,8]. This has been reported to occur via regulation of cell cycle protein and senescence markers [2]. The mechanisms underpinning these anti-proliferative properties elicited by 1,25-dihydroxyvitamin D_3 differ across different cell types and cell lines derived from the same type of cancer [2]. Some of the known effects induced by 1,25-dihydroxyvitamin D_3 are mediated through the nuclear vitamin D receptor (VDR), a transcription factor belonging to the superfamily of nuclear receptors for steroid hormones [9]. VDR is almost ubiquitously expressed throughout the human body, including the CNS, and functions by regulating over 500 genes by the ligated VDR protein's binding to vitamin D response elements, subsequently leading to gene activation and suppression [10]. Notably, increased levels of VDR expression have been reported in different cancer types, particularly in glioblastoma versus lower-grade gliomas [11]. More recent evidence also reports overexpression of a new oncogene, MED12, in glioblastoma patients which identifies as an important mediator of VDR signalling and an attractive target for future studies in the context of glioblastoma pathogenesis [12].

It is important to note that preclinical data reveal that the levels of 1,25-dihydroxyvitamin D_3 needed to significantly suppress cellular proliferation is greater than normal physio-

logical levels [13]. For example, the most active metabolite of the 1,25-dihydroxyvitamin D_3 hormone, calcitriol, exerts therapeutic effects at concentrations of 10^{-8} to 10^{-4} M [13], thus leading to serious side effects such as hypercalcaemia and possible complications during cancer treatment [2]. This has therefore led to the production of safer alternative synthetic analogues of 1,25-dihydroxyvitamin D_3, including tacalcitol, calcipotriol, ML-344, EM1, CB1093, EB1089, KH1060, MC903 and MC1288, all of which have proved to be able to induce anti-tumour activity in glioblastoma without giving rise to severe hypercalcemic side effects and bioavailability issues [1]. Importantly, synthetic vitamin D analogues have been shown to interact with the VDR [14], and are also reported to suppress cellular proliferation and viability in different cancer cells [15-17]. Evidence reported by Salomón et al. showed that glioblastoma associated with VDR expression is linked with a better long-term survival of patients, thus supporting a role for VDR in glioma progression [18]. The group also investigated the role of VDR in cellular survival, migration and/or invasion (i.e., important processes in glioma progression) using human glioblastoma T98G cells, a cell line that does express VDR. They found that silencing VDR in the T98G cell line significantly increased cellular survival, whereas supplementation with calcitriol (the active 1,25-dihydroxyvitamin D_3 hormone) subsequently increased VDR mRNA and protein levels and suppressed glioma cell survival [18]. Similarly, the ability of 1,25-dihydroxyvitamin D_3 to suppress migration and proliferation in the T98G human glioblastoma cells was reported by Emanuelsson et al. [19]. The group also demonstrated significant suppression of proliferation and migration of T98G cells by both calcipotriol and tacalcitol, with stronger effects observed with tacalcitol [19].

Vitamin D and Vitamin D Analogues: Modulators of glioma risk and progression

Clinicians commonly use circulating vitamin D (25-hydroxyvitamin D_3) to determine the index of vitamin D status in the body [20]. As defined by the Endocrine Society's Practice Guidelines of Vitamin D, circulating 25-hydroxyvitamin D_3 serum level in humans lower than 20ng/ml, from 20 to 30ng/ml, and higher than 30ng/ml are indicative of a deficiency, a relative insufficiency, and a sufficiency of vitamin D, respectively [21]. Interestingly, some epidemiological studies and clinical observations indicate a connection between vitamin D deficiency or low circulating 25-hydroxyvitamin D_3 serum levels (due to limited sun exposure essential to convert cholecalciferol to Vitamin D and/or poor dietary intake) to an increased risk of developing gliomas and put forth a potential application of this vitamin as a biomarker in glioblastoma prevention or earlier prognosis, reviewed in [16,22]. Epidemiological data also suggest a higher risk of brain tumours in adults, to winter births [16] and comparative studies on blood bank specimens correlate higher prediagnosis serum 25-hydroxyvitamin D_3 levels to lower risk of glioblastoma in men over age 56 years [23]. Glioblastoma patients with 25-hydroxyvitamin D_3 serum levels greater than 30ng/mL prior to initiation of chemotherapy and radiation demonstrate longer overall survival [16], highlighting the strong potential of supplemental vitamin D to reduce mortality in patients compared to non-users. Patients supplementing vitamin D following diagnosis of glioblastoma have also been reported to have a survival advantage [24].

Data from preclinical studies have highlighted the potential of combining the synergistic effects of 1,25-dihydroxyvitamin D_3 effects with other therapeutic options for glioblastoma. For example, one study showed that TMZ and vitamin D co-administration significantly inhibited tumour progression, concomitantly enhancing survival duration in rat glioblastoma orthotopic xenograft models, when compared to TMZ treatment alone [25]. However, despite extensive in vitro and animal studies in this field, limited small-scale clinical trials have been conducted to thoroughly evaluate the safety and efficacy of concomitant treatment with vitamin D or vitamin D on its own in the treatment of glioblastoma. A phase II clinical trial conducted by Trouillas et al., investigated adjunct alfacalcidiol (vitamin D analogue) administration in synergy with classical surgery–radiotherapy–chemotherapy treatments during treatment for malignant glioblastoma. The study reported safety of the supplementation in addition to induction of a progressive and durable regression of the tumour in some patients [26]. Ongoing phase I/II clinical trials are currently underway to determine the combinatorial effects of calcitriol with other chemotherapeutic agents on glioma and other brain tumours. In a phase I/II clinical trial, the efficacy and toxicity of long-term high-dose 1,25-dihydroxyvitamin D_3 (daily dose of 4000 IU) with concurrent chemoradiotherapy containing TMZ followed by adjuvant chemotherapy containing TMZ is being investigated in newly diagnosed glioblastoma patients (ClinicalTrials.gov Identifier: NCT01181193). In another phase 1 trial, the effectiveness, and maximum tolerated doses of subcutaneous and/or oral calcitriol combined with intravenous carboplatin is being investigated in the treatment of advanced solid brain tumours (ClinicalTrials.gov Identifier: NCT00008086).

Conclusion and future perspectives

Findings based on different mouse, rodent, and human glioma cell lines report that 1,25-dihydroxyvitamin D_3 and vitamin D analogues may promote cell cycle arrest, apoptosis, anti-migratory and anti-invasive effects in various types of brain cancer cells. These compounds also appear to function synergistically when combined with other cancer therapeutics for glioma. Although the preclinical and epidemiologic data are persuasive, the relevance of findings based on in vitro and preclinical studies must eventually be validated in well-designed human clinical trials to support the assertion of 1,25-dihydroxyvitamin D_3 as a complementary nutritional therapy in the treatment of glioblastoma. Furthermore, future research should also focus on the development of improved vitamin D analogues, which are efficient in low doses and safe for co-administration to glioblastoma patients whose tumours express a vitamin D-responsive receptor.

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