THE ROLE OF VITAMIN D SUPPLEMENTATION FOR HEAD AND NECK CANCER : A LITERATURE REVIEW

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head and neck cancer, quality of life, recurrence, vitamin D

ABSTRACT

Background: Vitamin D has several roles, namely physiological function of calcium and bone metabolism, cell growth and differentiation, immune and cardiovascular function. Vitamin D deficiency can cause the risk of cancer. Head and neck cancer is one of the cancers that occur due to vitamin D deficiency in the body. This literature review was to asses and evaluate the impact and benefits of vitamin D supplementation for head and neck cancer.
Discussion: A study found an association between vitamin D supplementation and a low risk of recurrence in conditions of high total vitamin D levels. Another study found a significant increase in quality of life (QOL). The primary mechanism of vitamin D action is mediated through binding of either 1,25(OH)2D3 (active form) or 25(OH)D (less active form) to the VDR, which is a member of the nuclear receptor superfamily of steroid and thyroid hormones with gene-regulatory and consequent anti-proliferative properties.
Conclusions: Vitamin D supplementation provides a role in improving the condition of patients with head and neck cancer. Both in terms of suppressing recurrence and in terms of increasing quality of life.

INTRODUCTION

Vitamin D is a steroid hormone, consisting of cholecalciferol (vitamin D_3) which is an endogenous form and synthesized in the skin by the action of ultraviolet light, and ergocalciferol (vitamin D_2) which is an exogenous form and is obtained through consumption of food or supplements[1–4]. In the liver and other tissues ergocalciferol and cholecalciferol are converted to 25(OH)D. Then 25(OH)D is metabolized to its active form 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] by 25-hydroxyvitamin D-1-α-hydroxylase, or CYP27B1. This hydroxylation occurs mainly in the kidneys, but extra kidney tissue and immune cells are also capable of producing 1,25$(OH)_2$D. The active form of Vitamin D (1,25-dihydroxyvitamin D) is a powerful immunomodulator with receptors in macrophages, monocytes T and B lymphocytes [5–8].

To determine vitamin D status Serum 25(OH)D was used, although the cut off value for classifying insufficiency/deficiency was inconsistent. However, a general definition for vitamin D status based on serum levels of 25(OH)D has been widely established and adopted: Deficiency < 20 ng/ml (50 nmol/l); insufficient 21-29 ng/ml (52-72 nmol/l); enough > 30 ng / ml (> 75 nmol / l) [4,9]. According to The National Academy of Sciences recommends the following daily intakes of vitamin D : 1 to 50 years, 5 µg (200 IU); 51-70 years, 10 µg (400 IU) is older than 71 years 15 µg (600 IU). In one study, 12,5 µg (500 IU) per day was associated with 30 ng / mL 25 (OH) D levels [10].

Vitamin D has many functions in terms of suppressing cancer through its various effects as antitumor, antiproliferative, apoptosis and angiogenesis. Therefore, individuals with low serum vitamin D levels will have a high risk of

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developing cancer. Head and neck cancers including oral cancer have a low response to chemotherapy and anti-cancer drugs. Therefore, it is very possible for resistance to chemotherapy and radiotherapy. Vitamin D is expected to provide a better response to cancer therapy and prevent recurrence[2,11–18].

Some studies show that vitamin D can play an important role in the incidence of cancer. It is estimated that vitamin D acts through vitamin D receptors (VDR) to produce anti-cancer effects and has the potential to regulate immune cells. This known transcription phenomenon is responsive to binding to vitamin D, expressed in many normal and malignant tissues, binds to target genes that regulate cell growth, and has been shown to be removed or lowered regulated in tumor tissue. Preclinical studies of the biologically active forms of vitamin D, 1,25$(OH)_2$D also support vitamin D-mediated antiproliferation and induce apoptosis of cancer cells[19,20].

To assess and determine the efficacy of vitamin D supplementation in the treatment of head and neck cancer in terms of reducing the risk of recurrence and improving quality of life.

LITERATURE REVIEW

Literature search was performed in PubMed and Google Scholar databases between January 2008 until September 2018. The following keywords were used in the search “vitamin D and oral cancer” or “vitamin D head and neck cancer”. Titles and abstract of each publication were repeatedly reviewed in the search process. The entire article was checked when necessary. To avoid any possible reports missed in the literature search, we reviewed references from relevant articles and related reviews to identify potensial relevant studies.

The inclusion criteria will be used for selecting articles as follows :

- English and Indonesian language articles published between January 2008 until September 2018
- Study type cohort study and randomized controlled trials (RCTs) with any dose or formulation of vitamin D intervention compared with placebo or no treatment

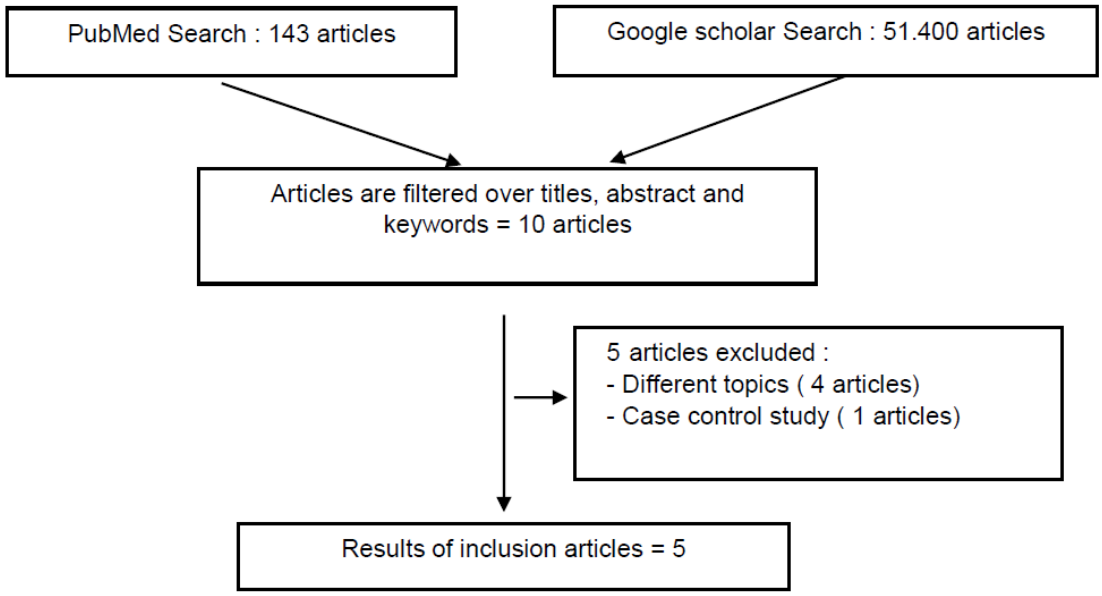

Figure 1 Flowchart of Study Selection

- Head and neck cancer based on requrrance and quality of life

Data extraction sumarized in 4 tables. There were two outcome measures we used in order to know the role of supplementation vitamin D in included studies. The first outcome was the requrrance of cancer and the second outcome was of quality of life.

Number of 51.543 articles we got from PubMed and Google scholar, we filter articles based on title, abstract and keywords to find 10 articles, then we read 10 articles in full text, 5 articles do not enter criteria, namely 4 articles not included in the title and 1 case study arti-

Tabel 1. Study Characteristic

NO.	Publication Year	Author	Title	Design Study	Area	Cancer
1	2009	Lyel Roh,Jong. et.al.[21]	Prevention of Post Operative Hypocalcemia With Routine Oral Calcium and Vitamin D Supplements in Patiens With Differentiated Papillary Thyroid Carcinoma Undergoing Total Thyroidectomy Plus Central Neck Dissection	Randomized Control Study	Republic of Korea	Papillary Thyroid Carcinoma
2	2010	Walsh, Jarrett E.et.al.[22]	Use of α,25-Dihydroxy Vitamin D Treatment to Stimulate Immune Infiltration Into Head and Neck Squamous Cell Carcinoma	Randomized trial	USA	HNSCC
3	2016	Wang, Lu.et.al.[23]	Longitudinal, Observational Study on Associations Between Postoperative Nutritional Vitamin D Supplementation and Clinical Outcomes in Esophageal Cancer Patients Undergoing Esophagectomy	Longitudinal observational study	China	Esophageal Cancer
4	2017	Anand, Akshay.et. al.[11]	Expression of Vitamin D Receptor and Vitamin D Status in Patients with Oral Neoplasm and Effect of Supplementation on Vitamin D Quality of Live in Advanced Cancer Treatment	Prospective Observational Study	India	OSCC
5	2018	Yokosawa, Eva B. et.al.[19]	Vitamin D Intake and Survival and Recurrence in Head and Neck Cancer Patients	Prospective cohort study	USA	HNC

Tabel 2. Sample Characteristic

NO.	Publication Year	Author	Age (year)	Subject	Sex (M/F)
1	2009	Lyel Roh,Jong.et.al.[21]	22 – 77	49	9 / 40
2	2010	Walsh, Jarrett E.et.al.[22]	45 – 92	16	9 / 7
3	2016	Wang, Lu.et.al.[23]	Mean Age 61	49	40 / 9
4	2017	Anand, Akshay, et al.[11]	Mean Age 42	24	N/A
5	2018	Yokosawa, Eva B. et.al.[19]	Mean Age 53-68	434	434 / -

cle. Therefore, the author gets 5 articles that match the inclusion criteria.

The 5 articles that the research design obtained, the following were two RCT (Randomized Control Study) designs and three Cohort research designs (longitudinal observational studies, prospective observational studies, and prospective cohort studies). The type of head and neck cancer that occurs is papillary thyroid carcinoma, head and neck squamous carcinoma, esophageal cancer, oral squamous cell carcinoma and head and neck cancer (Table 1). The articles was published in 2009 until 2018. Total sample 572 peoples, with male gender as many as 492 people and women as many as 56 people for 4 articles because 1 article does not explain about gender. The sample age range is 22-92 years (Table 2).

Supplementation of vitamin D varies as low as 1 µg per day and the largest is 25 µg per day. The outcome of reducing recurrence can be seen in 3 authors, Yokosawa, Eva B. et.al.[19], Lyel oh, Jong.et.al.[21], Walsh, Jarrett E.et.al.[22] and the outcome of improving quality of life can be seen from 3 authors namely Anand, Akshay, et al.[11], Lyel Roh, Jong.et.al.[21] and Wang, Lu.et.al.[23] (Table 3 and Table 4).

Yokosawa, Eva B, et al. found that recurrence occurred in 9.2% of patients who received vitamin D supplementation of more than 16.875 µg per day and 12.96% of recurrences occurred at vitamin D supplementation of less than 5 µg per day[19] (Tabel 3).

Tabel 3. Supplementation Dose and Recurrance Risk Outcome

No.	Author	Supplementation Vitamin D per oral (Dose)	Recurrence
1	Yokosawa, Eva B. et.al.[19]	< 5 - ≥ 16,875 µg	- Recurrance was seen in 9.2 % patient with ≥ 16,875 µg supplementation vitamin D - 14,7 % patient with 11,625 µg - ≤ 16,875 µg - 17,6 % with 5 µg - ≤ 11.625 µg - 12.96 % with ≤ 5 µg supplementation with vitamin D
2	Lyel Roh,Jong.et.al.[21]	Calcium 3 g/Day and vitamin D 1 µg/Day (administered as 0,5 µg twice daily)	Reccurence developed in the lateral neck (0,5 %)
3	Walsh, Jarrett E.et.al.[22]	4 µg/Day	Patient group who received vitamin D treatment had a longer time to recurrence than no treatment.

Tabel 4. Supplementation Dose and Quality of Life Outcome

No.	Author	Supplementation vitamin D per oral (Dose)	Quality of life
1	Anand, Akshay, et al. [11]	Vitamin D 25 µg / Day	Quality of Life improved with supplementation Vitamin D
2	Lyel Roh,Jong.et.al.[21]	Calcium 3 g/Day and vitamin D 1 µg/Day (administered as 0,5 µg twice daily)	Hypocalcemia symptoms were minimal in supplementation calcium and vitamin D
3	Wang, Lu.et.al.[23]	5-10 µg/Day	Vitamin D supplementation had higher scores of physical functioning, social functioning, and global health

DISCUSSION

Geographical variation is very important in terms of mortality in cancer, which is associated with latitude and ultraviolet-B radiation in the sun. Photosynthesis of vitamin D_3 (cholecalsiferol) occurs in the skin by the action of ultraviolet-B radiation in the sun. Overall vitamin D status in a person depends on cholecalciferol and ergocalciferol (Vitamin D_2). 25-Dyhydroxyvitamin D, is a major form of circulation of vitamin D, reflecting the cumulative effect of sun exposure and dietary intake of vitamin D [1–4,24,25].

The primary mechanism of vitamin D action is mediated through binding of either $1,25(OH)_2$ D_3 (active form) or 25(OH)D (less active form) to the VDR, which is a member of the nuclear receptor superfamily of steroid and thyroid hormones with gene-regulatory and consequent anti-proliferative properties[2]. Binding of $1,25(OH)_2D$ to the VDR (either in the cell nucleus or in the cytoplasm) promotes association of the VDR–$1,25(OH)_2D$ complex with the retinoid X receptor (RXR)[2]. The $1,25(OH)_2D$–VDR–RXR complex binds to vitamin D-response elements in DNA which operate to initiate gene transcription. Activation of the VDR by $1,25(OH)_2D$ can restore or enhance proapoptotic effects in different cancer cells through transcriptional activation of bax and p-calpain, two effective proapoptotic proteins. VDR–vitamin D activation also been demonstrated to increase mRNA expression of transforming growth factor, a potent antiproliferative cytokine in normal and early stage cancer cells; superoxide dismutase, which may reduce oxidative stress-induced DNA damage and loss to DNA repair mechanisms that contribute to carcinogenesis and inflammatory cytokine production; as well as cyclin-dependent kinase (CDK) inhibitor p21, RBL2, RBLP6 and forkhead box O (FOXO) tumour suppressors that function to counteract MAPK-mediated phosphorylation and growth[2]. VDR activation may also facilitate transcriptional repression of Bc1-2 and telomerase (pro-survival proteins), as well as CDK1 mRNA, which encodes a required protein for cellcycle progression. Suppression of vascular endothelial growth factor, responsible for angiogenesis, as well as the pro-inflammatory cyclooxygenase-2, was also observed. In addition, 1,25(OH)2D may disrupt the function of β-catenin, the terminal mediator of Wnt signalling, which activates transcription of genes whose protein products (c-Myc and cyclin D1) control cell proliferation, as well as insulin-like growth factor–stimulated tumour growth[2].

A study found an association between vitamin D supplementation and a low risk of recurrence in conditions of high total vitamin D levels[19]. Another study found a significant increase in quality of life (QOL) and Disease-Free Survival (DFS) in esophageal cancer (EC) patients who underwent esophagectomy who received vitamin D supplementation during cancer treatment and post recovery[23]. T-cell functional competence is very important to stimulate antitumor immune reactivity. However, patients with head and neck squamous cell carcinoma have low immunity. There are several immune inhibitory mechanisms mediated by HNSCC (Head and Neck Squamous Cell Carcinoma), including the induction of their immune suppressing cells that block the host's immune reactivity. This study shows that treatment of patients with advanced HNSCC disease with vitamin D supplementation reduces the level of immune inhibitory CD34 cells in peripheral blood and simultaneously increases peripheral blood cell immune reactivi-

ty[22]. Likewise, prior study said that low vitamin D levels are closely related to the risk of neck and head cancer, then he said that vitamin D supplementation significantly improved healing of erythema, lichenoid, edema, ulceration and pain in patient oral cancer [11].

There are many benefits of vitamin D for body health. Therefore, we must always keep vitamin D levels in the body in sufficient condition. In addition to providing preventive benefits in the prevention of infections, cardiovascular disorders, and cancer[26]. Vitamin D supplementation provides curative benefits in cancer patients in terms of suppressing the cancer itself, preventing recurrence and improving quality of life[11,19,21–23].

CONCLUSION

Vitamin D supplementation provides a role in improving the condition of patients with head and neck cancer. Both in terms of suppressing recurrence and in terms of increasing quality of life. But unfortunately there is still few research on vitamin D supplementation on oral cancer or head and neck cancer, therefore more researchers are expected to conduct research related to the role of vitamin D, especially in terms of oral cavity health.

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