RESEARCH ARTICLE

Vitamin D Deficiency Associated with Differentiated Thyroid Carcinoma: A Case- Control Study

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Abstract

Objective: In recent decades, the incidence of thyroid cancer has increased throughout the world. It is unclear whether factors such as vitamin D deficiency may have been involved in this increase. The present case-control study was conducted to examine any association between Vitamin D deficiency and thyroid cancers. **Methods:** The study was conducted on 85 patients with differentiated thyroid cancer diagnosed based on fine needle aspiration biopsy as the case group and 85 healthy controls. Serum levels of vitamin D were evaluated before thyroidectomy. For each patient in the case group, one healthy euthyroid person without any thyroid nodules from the general population matched based on season, sex, age (± 1 year) and BMI (± 1) was selected. Finally, 85 pairs were obtained considering inclusion and exclusion criteria. Thyroid function, thyroid antibodies and serum vitamin D were assessed and thyroid sonography was performed in all participants. **Results:** In the patient group, 72 (85%) were female and 13 (15%) were male. The mean (SD) serum vitamin D level was 8.00 (±3.7) in patient group, as compared to 13.4 (±7.90) in the control group, the difference being significant (OR: 6, 95 % CI: 1.02-113.3; P=0.046). **Conclusion:** A significant association was noted between vitamin D deficiency and differentiated thyroid cancer. Further studies with a prospective design are necessary to further define the roles of this factor.

Keywords: Vitamin D- thyroid cancer- etiology

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Introduction

Thyroid cancer is the most common cancer in endocrine system worldwide. Based on recent data, thyroid cancer is the fifth most common cancer in women. This malignancy accounts for 1.3% of cancer diagnosis with 0.5% of cancer-related mortalities each year. Thyroid cancers include undifferentiated cancers with high mortality, such as anaplastic cancers and differentiated cancers with good prognosis such as papillary thyroid carcinoma and follicular cancer. Differentiated thyroid cancers consists more than 90% of all thyroid cancers (Davis et al., 2015; Tuttle et al., 2014; Jemal et al., 2011).

In recent years incidence of thyroid cancer has increased around the world (Amphlett et al., 2013; Colonna et al., 2015; Jung et al., 2017; Kent et al., 2007). It is predicted that by 2019, papillary thyroid cancer is the third most common cancer in women (Enewold et al., 2009). The fact that the increased incidence of thyroid cancer is caused by the increase in the use of tools such as thyroid sonography or other imaging techniques, or the incidence of thyroid cancer has actually increased for unknown reasons, is not clear. In addition to the increased incidence of small cancers diagnosed during sonography, large cancer incidence has also increased. Despite the early detection of thyroid cancer, the related mortality has increased, too (Dom et al., 2012; Meinhold et al., 2010). Therefore, other factors could be involved. Currently, the known risk factors for thyroid cancer are: a family history of thyroid cancer, history of head and neck radiation in childhood, exposure to ionizing radiation and the use of inadequate or excessive iodine. But none of these can explain the recent increase in the incidence of thyroid cancer. More recently, other factors such as chemical toxins (Borena et al., 2011; Zhao et al., 2012), insulin resistance (Rezzonico et al., 2009), metabolic syndromes, obesity and diabetes (Biondi et al., 2012; Pellegriti et al., 2009), nutritional factors (Jung et al. 2013; Clero et al., 2012), and vitamin D deficiency (Roskies et al., 2012; Stepien et al., 2010), have been proposed as potential risk factors for thyroid cancer.

The role of vitamin D deficiency in the pathogenesis of breast, colon, prostate and pancreatic cancer has been suggested (Deeb et al., 2007). Association between

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vitamin D and thyroid cancer in humans is not clear, some previous articles have demonstrated the association between Vitamin D deficiency and thyroid cancer (Roskies et al.,2012; Stepien et al., 2010), while other studies have not shown such a relationship (Laney et al., 2010; Jonklaas et al., 2013).

However, studies on the effect of vitamin D on the thyroid cancer are limited. The aim of this study was to investigate the relationship between serum levels of vitamin D and thyroid cancers and assess the role of this parameter as a potential new risk factor in the incidence of thyroid cancer.

Materials and Methods

This case-control study was performed on 85 euthyroid patients with differentiated thyroid carcinoma. Inclusion criteria were: 1) Euthyroidism (normal thyroid function was defined as normal thyroid stimulating hormone [TSH: 0.4-4.2 mIU/L], normal free thyroxine [FT4: 0.8-1.8 ng/dL] and normal triiodothyronine [FT3: 2.3-4.2 pg/ml] levels); 2) thyroid nodules with a size of more than 1 cm; 3) anti-TPO and anti-Tg negative titers (antithyroid peroxidase antibody < 16 IU/ml and antithyoglobulin < 100 IU/ml) and 4) malignancy or suspicious for malignancy in FNAB (fine needle aspiration biopsy) based on Bethesda system.

Patients with a history of thyroid disease, patients who were received thyroid drugs at any time, patients with a history of head and neck radiation or thyroid surgery, patients who used contrast over the past 6 months, smokers, patients who were received statins, antihypertensive medications or supplements that contain vitamin D and patients with liver, kidney or neurological disease or advanced psychological disorders that may affect the thyroid function tests, were excluded. Pregnant women or nursing mothers were also excluded from the study. Eighty-five patients with differentiated thyroid Carcinoma (according to FNAB) who lived in iodine-sufficient areas (Delshad et al., 2010), were selected as case group. These patients were evaluated within January 2013 to June 2016 in Zahedan Endocrinology Clinic. In all patients, after thyroidectomy, positive permanent pathology confirmed the diagnosis. For each of the 85 patients of case group, a pair was selected from general population based on matching protocol: they were individually matched according to season, sex, age (±1 year) and BMI (±1) the cases. Thyroid function tests and thyroid ultrasonography were performed in all participants. Thus, 85 healthy euthyroid control participants were chosen with normal thyroid sonography. Individuals with any known acute or chronic illness were excluded. Finally, 85 pairs were obtained considering the above-mentioned inclusion and exclusion criteria. The Zahedan University Ethics Committee for Human Studies approved the protocol (ethical code number: 92-5788). All participants provided informed consent.

Body weight was measured without shoes and with light clothing using digital scale (in kilograms) and height was measured (in centimeters) in standing position without shoes. BMI (Body Mass Index) was calculated using the formula: weight (in kilograms) divided by the square of height (in meters). After 12 hours of fasting, blood samples were collected between 8 to 9 am. All samples were stored at -70 ° C until examination. FT4, FT3 and TSH using immunochemoluminescent assays by an automated analyzer (Diagnostic Products LIAISON, 2011, Italy).

Antithyroidperoxidase (normal range < 16 U/ml) and antithyroglobulin (normal range < 100) was measured by immunochemoluminescent assays employing commercial kits (Diagnostic Products LIAISON).FT4, FT3, TSH was measured byimmunochemoluminescent method, using an automatic analyzer (Diagnostic Products LIAISON, 2011, Italy). Thyroid antibodies were measured by immunochemoluminescent and commercial kits (Diagnostic Products LIAISON). 25 hydroxy vitamin D (25 OHD) was measured, using enzyme immunoassay method (EIA) [immunodiagnostic system; IDS (LTD), UK]. Values less than 20 ng/ml were considered as vitamin D deficiency (Holick, 2007).

Thyroid sonography was performed for all participants using a 7.5 MHz linear probe by a sinologist (Aloka Co. Ltd., Tokyo, Japan). All patients with nodules more than one centimeters, who were FNAB eligible, were under FNAB. In the control group members there were no nodules with any sizes. All FNAB samples were analyzed by an experienced pathologist. All malignant or suspicious cases, according to the Bethesda system, were included. After thyroidectomy, permanent pathology confirmed the diagnosis.

Statistical analysis

Continuous variables were presented as mean (standard deviation) and categorical variables as count (percentage). Pair-matched analysis only relies on discordant pairs (exposed case-unexposed control and unexposed case-exposed control) and these involve small counts in our study as the sample size is not large and more importantly the prevalence of exposure is very high (vitamin D deficiency). So the standard conditional logistic regression model required for matched analysis is susceptible to sparse-data bias (Mansournia et al., 2013). Following Greenland et al, we performed penalized conditional logistic regression using a F(2,2) prior for the matched odds ratio (Greenland and Mansournia, 2015; Greenland et al., 2016). The F(2,2) prior encodes the 95% prior odds ratio interval of 1/39 to 39. To apply F(2,2) prior, we augmented the original dataset with two sets of discordant pairs: one containing an exposed case and an unexposed control; the other with an unexposed case and an exposed control where the exposure was vitamin D deficiency (1: 25 OHD < 20, 0: 25 OHD ≥ 20). Based on Greenland et al suggestion, we presented 95% profile-likelihood confidence intervals for odds ratios along with P-values based on likelihood-ratio tests (Greenland et al., 2016). All analyses were performed using Stata version 12 (Stata Corporation, College Station, TX).

Results

Demographic characteristics of the study population are shown in Table 1. This survey included 85 patients

Table 1. Clinical and Laboratory Characteristics of Study Subjects*

Variables	Case group (n=85)	Control group (n=85)
Sex (female), n (%)	72 (85)	72 (85)
Age (years)	31.24 (11.36)	31.94 (12.27)
BMI (kg/m^2)	27.9 (5.7)	27.1 (5.8)
TSH (mIU/l)	2.2 (1.1)	2.1 (1.3)
Ft4 (ng/ml)	1.1 (0.3)	1.0 (0.2)
FT3 (pg/ml)	2.7 (0.7)	2.6 (0.5)
Anti TPO (IU/mL)	6.3 (4.1)	5.6 (4.7)
Anti Tg (IU/mL)	27.2 (20.9)	25.4 (27.3)
25 OHD (ng/ml)	8.0 (3.7)	13.4 (7.9)
Vitamin D deficiency, n(%)	30 (100)	25 (83.3)

*Mean (SD), except where otherwise indicated; BMI, body mass index; TSH, thyroid stimulating hormone; FT4, free thyroxin; FT3, free triiodothyronin; Anti-TPO, antithyroid peroxidase; Anti-Tg, antithyroglobulin; 25 OHD, 25 hydroxy vitamin D.

and 85 matched controls based on season, sex, age (± 1 year) and BMI (± 1). In the group of patients, there were 72 (85%) females and 13 (15%) males. The mean (SD) of age was 31.24 (11.36) in the case group and 31.94 (12.27) in control group. Serum FT4, FT3, TSH, Anti-TPO, Anti-Tg concentrations were in the normal range in both groups and no significant difference was observed between the two groups.

The average of vitamin D serum level was 8.0 ± 3.7 ng/ml in the case group and 13.4 ±7.9 ng/ml in the control group ($p < 0.001$).

The matched Tables 2 shows the distribution of vitamin D deficiency (1: 25 OHD < 20, 0: 25 OHD ≥ 20) in 85 matched case-control pair. There was a significant association between vitamin D deficiency and differentiated thyroid cancer (penalized OR = (15+1)/(1+1) = 8, 95 % CI: 2.28-50.6; P= 0.006).

Discussion

In this study, we investigated the association between serum 25 OHD levels and differentiated thyroid cancer (DTC) in an Iranian population. Our study suggested that higher serum 25 OHD levels were associated with decreased risk of thyroid cancer. As mentioned above, we classified subjects into two groups based on 25OHD value in this study. The odds of DTC in the vitamin D deficient group (serum 25 OHD levels lower than 20 ng/ml) was significantly (8-fold) higher than that of in the subjects with 25OHD levels higher than 20 ng/ml. We note that 95% confidence interval of (2.28-50.6) is a bit wide even after penalization as the number of one type of discordant pair in Table 2 is very low (1) and the prior F(2,2) is weakly informative as it corresponds to 95% prior odds ratio interval of 1/39 to 39 (Greenland and Mansournia, 2015; Greenland et al., 2016).

The incidence of thyroid cancer has increased in the past decade across the globe (Amphlett et al., 2013; Colonna et al., 2015; Jung et al., 2017; Kent et al., 2007; Enewold et al., 2009; Haggar et al., 2012; Ellison and Wilkins, 2012; Dal Maso et al., 2011). TSH is the main regulator of cell growth and differentiation in thyroid and also is a mitogen on cell cultures and can reduce apoptotic cell death in response to various factors (Rapoport et al., 1998). In our study, serum levels of TSH were in the normal range and there was no significant difference between thyroid cancer patients and healthy control group. Therefore, our results cannot be explained by TSH.

Table 2. Vitamin D Deficiency (25OHD < 20 ng/ml) in 85 Patients with Thyroid Carcinoma and 85 Pair-matched Controls

Case	Control		
	25OHD < 20 ng/ml	25OHD ≥ 20 ng/ml	
25OHD < 20 ng/ml	69	15	
25OHD ≥ 20 ng/ml	1	0	85

The relationship between serum 25OHD and thyroid cancer has been the subject of some recent studies. We found a positive association between levels of vitamin D and thyroid cancer. The prevalence of Vitamin D deficiency in thyroid cancer patients was more, compared to the control group. Our results are in accordance with previous studies which showed an association between Vitamin D deficiency and thyroid cancer (Roskies et al., 2012; Stepien et al., 2010). But on the other hand, other studies have not reported any association between low levels of vitamin D and differentiated thyroid cancer (Laney et al., 2010; Jonklaas et al., 2013). Some studies have demonstrated the association between Vitamin D deficiency and solid tumors such as colon cancer (Garland et al., 2006), breast cancer (Abbas et al., 2008), and prostate cancer (Ahonen et al., 2000). Anti-cancerous effects of vitamin D, such as increasing apoptosis, stopping the cell cycle, inhibition of proliferation and promoting differentiation and decreasing invasiveness, been identified (Laney et al., 2010; Hansen et al.,2001; Giovannucci, 2008).

Known factors that can affect the serum levels of vitamin D, such as race, BMI, season, autoimmunity and vitamin D supplements was measured in this study and were not different between the two groups. Having a control group without thyroid nodules, thyroid nodules histopathological evaluation, in addition to cytological evaluation, measurement of thyroid antibodies and matching the groups by gender, age, BMI and the season of sampling were the advantages of this study. But this study, was a cross-sectional observation study, therefore a causal relationship between vitamin D deficiency and thyroid cancer cannot be made.

In conclusion, patients with differentiated thyroid cancer have lower serum 25 OHD level. There is an association between vitamin D deficiency and differentiated thyroid cancer. Including larger sample size in a prospective design may improve the strength of future studies. More investigations are required to define the role of this factor in malignant thyroid nodule formation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication

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References

Abbas S, Linseisen J, Slanger T, et al (2008). Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. *Carcinogenesis*, **29**, 93-9.

Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P (2000). Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control*, **11**, 847-52.

Amphlett B, Lawson Z, Abdulrahman GO, et al (2013). Recent trends in the incidence, geographical distribution, and survival from thyroid cancer in Wales, 1985-2010. *Thyroid*, **23**, 1470-8.

Biondi B, Arpaia D, Montuori P, et al (2012). Under the shadow of vesuvius: a risk for thyroid cancer?. *Thyroid*, **22**, 1296-7.

Borena W, Stocks T, Jonsson H, et al (2011). Serum triglycerides and cancer risk in the metabolic syndrome and cancer (Me-Can) collaborative study. *Cancer Causes Control*, **22**, 291-9.

Clero E, Doyon F, Chungue V, et al (2012). Dietary patterns, goitrogenic food, and thyroid cancer: a case-control study in French Polynesia. *Nutr Cancer*, **64**, 929-36.

Colonna M, Uhry Z, Guizard AV, et al (2015). Recent trends in incidence, geographical distribution, and survival of papillary thyroid cancer in France. *Cancer Epidemiol*, **39**, 511-8.

Dal Maso L, Lise M, Zambon P, et al (2011). Incidence of thyroid cancer in Italy, 1991-2005: time trends and age-period-cohort effects. *Ann Oncol*, **22**, 957-63.

Davies L, Morris LG, Haymart M, et al (2015). American association of clinical endocrinologists and American college of endocrinology disease state clinical review: The increasing incidence of thyroid cancer. *Endocr Pract*, **21**, 686-96.

Deeb KK, Trump DL, Johnson CS (2007). Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer*, **7**, 684-700.

Delshad H, Mehran L, Azizi F (2010). Appropriate iodine nutrition in Iran: 20 years of success. *Acta Med Iran*, **48**, 361-6.

Dom G, Tarabichi M, Unger K, et al (2012). A gene expression signature distinguishes normal tissues of sporadic and radiation-induced papillary thyroid carcinomas. *Br J Cancer*, **107**, 994-1000.

Ellison LF, Wilkins K (2012). Canadian trends in cancer prevalence. *Health Rep*, **23**, 7-16.

Enewold L, Zhu K, Ron E, et al (2009). Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev*, **18**, 784-91.

Garland CF, Garland FC, Gorham ED, et al (2006). The role of vitamin D in cancer prevention. *Am J Public Health*, **96**, 252-61.

Giovannucci E (2008). Vitamin D status and cancer incidence and mortality. *Adv Exp Med Biol*, **624**, 31-42.

Greenland S, Mansournia MA (2015). Penalization, bias reduction, and default priors in logistic and related categorical and survival regressions. *Stat Med*, **34**, 3133-43.

Greenland S, Mansournia MA, Altman DG (2016). Sparse data bias: a problem hiding in plain sight. *BMJ*, **352**, i1981.

Haggar FA, Preen DB, Pereira G, Holman CD, Einarsdottir K (2012). Cancer incidence and mortality trends in Australian adolescents and young adults, 1982-2007. *BMC Cancer*, **12**, 151.

Hansen CM, Binderup L, Hamberg KJ, Carlberg C (2001). Vitamin D and cancer: effects of 1,25(OH)2D3 and its analogs on growth control and tumorigenesis. *Front Biosci*, **6**, 820-48.

Holick MF (2007). Vitamin D deficiency. *N Engl J Med*, **357**, 266-81.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Jonklaas J, Danielsen M, Wang H (2013). A pilot study of serum selenium, vitamin D, and thyrotropin concentrations in patients with thyroid cancer. *Thyroid*, **23**, 1079-86.

Jung SK, Kim K, Tae K, Kong G, Kim MK (2013). The effect of raw vegetable and fruit intake on thyroid cancer risk among women: a case-control study in South Korea. *Br J Nutr*, **109**, 118-28.

Jung KW, Won YJ, Oh CM, et al (2017). Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2014. *Cancer Res Treat*, **49**, 292-305.

Kent WD, Hall SF, Isotalo PA, et al (2007). Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. *CMAJ*, **177**, 1357-61.

Laney N, Meza J, Lyden E, et al (2010). The prevalence of vitamin D deficiency is similar between thyroid nodule and thyroid cancer patients. *Int J Endocrinol*, **2010**, 805716.

Mansournia MA, Hernan MA, Greenland S (2013). Matched designs and causal diagrams. *Int J Epidemiol*, **42**, 860-9.

Meinhold CL, Ron E, Schonfeld SJ, et al (2010). Nonradiation risk factors for thyroid cancer in the US radiologic technologists study. *Am J Epidemiol*, **171**, 242-52.

Pellegriti G, De Vathaire F, Scollo C, et al (2009). Papillary thyroid cancer incidence in the volcanic area of Sicily. *J Natl Cancer Inst*, **101**, 1575-83.

Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM (1998). The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. *Endocr Rev*, **19**, 673-716.

Rezzonico JN, Rezzonico M, Pusiol E, Pitoia F, Niepomniszcze H (2009). Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. *Metab Syndr Relat Disord*, **7**, 375-80.

Roskies M, Dolev Y, Caglar D, et al (2012). Vitamin D deficiency as a potentially modifiable risk factor for thyroid cancer. *J Otolaryngol Head Neck Surg*, **41**, 160-3.

Stepien T, Krupinski R, Sopinski J, et al (2010). Decreased 1-25 dihydroxyvitamin D3 concentration in peripheral blood serum of patients with thyroid cancer. *Arch Med Res*, **41**, 190-4.

Tuttle RM, Haddad RI, Ball DW, et al (2014). Thyroid carcinoma, version 2.2014. *J Natl Compr Canc Netw*, **12**, 1671-80.

Zhao ZG, Guo XG, Ba CX, et al (2012). Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. *J Int Med Res*, **40**, 2041-50.