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ARTICLE REVIEW: VITAMIN D DEFICIENCY IN THYROID DISORDER (HASHIMOTO THYROIDITIS)

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ABSTRACT:

Vitamin D is primarily responsible for bone metabolism and phosphorus-calcium homeostasis. Previous studies revealed the close association of vitamin D deficiency with autoimmune disease such as Hashimoto thyroiditis. But the pathological mechanism is still under discussion. This systematic review included 25 datasets out of a total of 55. Of them, 20 database excluded due to duplication and 10 database excluded after title and abstracts. The analysis of Hashimoto was based on 25(OH) D level <20 ng/m counted as vitamin D deficiency. The prevalence of 25(OH) D in the HT group was observed higher (56.5%) as compared to non-HT (control) group. Moreover, the correlation between vitamin-D receptor gene polymorphisms (VDR) and risk of Hashimoto's thyroiditis was evaluated in present review. The statistical analysis indicate that HT was significantly associated with being female, age, sample size, study design, BMI, vitamin-D assay route, and mean value of vitamin D deficiency in HT and non HT patients. Our results suggest the positive association between vitamin D deficiency and Hashimoto thyroiditis. However, the relationship between vitamin D deficiency and HT was only prominent among population ≥30 year's age.

Keywords: Vitamin D deficiency, 25(OH) D, Hashimoto Thyroiditis, HT, systematic review, Autoimmune.

INTRODUCTION:

Vitamin D is mainly considered as vital nutrient in scientific pharmaceutical and modern population from recent years [1, 2]. A fat soluble nutrient present in human body and perform like pro hormonal function. Vitamin D is a predominantly essential nutrient that the physical body of human being needs to work appropriately. Moreover, it performs a significant function in rheumatologically health care owing to its entanglement in the phosphorus and calcium homeostasis. [3-5]. By considering above advantage, deficiency of vitamin D becomes the worldwide health issue in cohorts, all age groups, even in tropical regions with adequate ultraviolet irradiation or advanced economies with a long record of vitamin D food fortification potential strategies. Accommodating low level of vitamin D in human body might be destructive for diverse range of health population, such as lowering immune system potential, hazards of osteoporotic, risk of cardiovascular diseases, risk of stress fractures and cause tumors [6]. Plenty of previous evidence illustrate that the subject is continual evolving [3]. Various researches from fundamental science to clinical outcomes have emphasized a powerful correlation with acute disorders, as well as critical conditions. Besides, the huge quantity of observational statistics now accessible is also supported by the pathophysiological relationship of vitamin D with the regulation of immune, energy homeostasis, and regulation of the endocrine systems [7]. Earlier analyses have suggested that almost one billion populations across the globe have been diagnosed with low level of vitamin D [8]. Currently, vast observational data have indicated

that approximately of 40 % European population are vitamin D deficient, and about 13% United state population are severely deficient with vitamin D. In addition, South Asia had a prevalence of vitamin D deficiency of 70 % or more, while Southeast Asia had a prevalence of 6-70% [9]. Vitamin D deficiency is a widespread health problem, according to experts from all over the world; even in regions where there is sufficient sun light but no diverts consumption. All health risk elements of deficiency of vitamin D include malnutrition, aging, obesity, lack of sun exposure, female sex, dark skin pigmentation and winter season.

This adverse situation is aggravated by extensive interests about the deleterious effects of sun exposure, the usage of sunscreens, and the passive lifestyle of modern communities with a capacity to devour extra time indoors [3, 10]. Over the past ten years, several researches have demonstrated that low serum level of vitamin D are linked with a series of disorders including high blood pressure, diabetes, mood disorders, heart diseases, multiple sclerosis, cancer, and autoimmune thyroid disorders [11]. Moreover, some other chronic diseases such as kidney diseases, infections, cardiovascular and musculoskeletal had been also reported.

Among all autoimmune disorders, thyroid is one of the most vital organs in human body that possess a receptor for vitamin D nutrient. The thyroid vitamin D receptor is a part of substantial group of receptors known as nuclear receptors, which also associate to receptor for thyroid hormones. According to recent research, vitamin D receptor asserted on lymphocytes where it govern the differentiation and proliferation, evolving thyroid destruction and revealed correlation of vitamin D deficiency with thyroid disorders [12]. The thyroid diseases linked with massive endocrine system referred as thyroid glands. The thyroid gland is one of the main secretary organ which have many functions in homeostatic control such as energy consumption, metabolism and body growth [13, 14]. Each thyroid disorder could happen in a group of metabolic illnesses [15]. Now a days, Hashimoto is one of the familiar widespread autoimmune and acquired hypothyroidism disease that effects both adults and children [16]. Vitamin D deficiency is the main cause of Hashimoto disorder in autoimmune thyroid disease. There are a lot of studies that describe the role of low serum of vitamin D in autoimmune thyroid diseases such as hypothyroidism, AITD and Graves's disease. As a result, adequate awareness to vitamin D insufficiency diagnosis is required for therapy in order to the negative consequences on human nature. Vitamin D testing and supplementation have become increasingly popular in recent years. However, broad interventional researches have been inefficient to establish a clear effect, the role of vitamin D supplementation, as well as the optimal vitamin D dose and status, therefore, it is currently a point of discussion (in mostly vitamin D replete societies). Maximum studies did not confront the fundamental traits of a nutrient intervention survey, including too small sample sizes, vitamin D-replete populations, and incompatible intervention strategies regarding dose and metabolites, which might be ascribed to trial design flaws [7, 17, 18].

The supposed correlation between serum vitamin D and thyroid disorders has been documented in recent research [18]. The supposed correlation between serum vitamin D and thyroid disorders has been documented in recent research [19] However, several studies have not found a definite link between vitamin D deficiency and thyroid disorders, particularly Hashimato disease. Hashimato disorder's significance mechanism and prevalence are currently being debated [20]. The goal of this study is to compile recent research on the potential association between low vitamin D and thyroid disorders, such as HT and thyroid malignancies [16]. Furthermore, interventional

regimens have employed a one-size-fits-all technique, disregarding individual differences in body mass index (BMI) and vitamin D metabolism.

The main aim of present review is to evaluate the prevalence of vitamin D deficiency in Hashimoto thyroiditis (HT) and healthy group (Non-HT) patients. Even though pathological mechanism of low level of 25(OH) D was under discussion, a conscious effort was continued to find the association between vitamin D deficiency and Hashimoto thyroiditis.

We conduct a systematic review of literature, to find the association between vitamin D deficiency and Hashimoto thyroiditis. The search was up to date from 2017-2021 and describe current status. Four different database searching strategies were used including Google scholar, Pub Med, Scopus, ISI and web of science. Sample papers included patients age younger than 18 years between 30-50 years with Hashimoto thyroid. Other factors such as age, gender, 25(OH) D, season of sample and body mass index with higher level of thyroid antibodies TbO and TgO were incorporated. The references included in previously published review articles were also scanned, and any relevant papers were also included. The dataset papers based on pregnancy, cardiovascular disease, liver disease, vitamin D supplementation treatment and review papers were excluded before screening. Various keywords were employed to find articles such as Hashimoto's thyroiditis, 25-hydroxy vitamin D, vitamin D deficiency and hyperthyroidism.

Defining Vitamin D Deficiency:

Vitamin D's significance as an immune modulator system has been highlighted and deficiency of this hormone have been linked to a number of autoimmune disorders. Vitamin D works by binding to the vitamin D receptor and activating genes that respond to it. A variation in the VDR gene has been related to autoimmune thyroid disorders [21]. Nearly half of the world's population suffers from vitamin D deficiency. There are two types of vitamin D. Vitamin D2 is produced by irradiating the yeast sterol ergosterol with ultraviolet light, and it is established naturally in sun detected mushrooms. Because ultraviolet light from the sun causes vitamin D3 to be synthesised by humans, it is the most "natural" type. Vitamin D2 is not produced by humans, although it is found in most oil-rich fish such as mackerel, salmon, and herring. The Institute of Medicine recently defined that a 25(OH) D of >0.8IU is considered vitamin D deficiency. A 25(OH)D of 21–29 ng/mL is considered vitamin D insufficiency [22].Vitamin D deficiency is related to weak skeletal outcomes (serum 25-hydroxyvitamin D [25(OH)D] 50 nmol/L or 20 ng/ml). A 25(OH)D concentration of less than 30 nmol/L or 12 ng/ml indicates severe vitamin D deficiency [7]. According to the Korea National Health and Nutrition Examination Survey, about 80% of the Korean population had levels of vitamin D between 10 and 30 ng/mL, with 10% having levels less than 10 ng/mL [23] .

Vitamin D levels less than 8 ng/mL were considered severe, 9 to 15 ng/mL concentrations were considered mild, greater than 16-20 ng/mL concentrations were regarded vitamin D insufficiency, and >20 ng/mL concentrations were regarded normal vitamin D levels [16]. Despite the fact that the bioavailable fractions of vitamin D metabolites may be more therapeutically useful, serum 25(OH)D is regarded the best marker for measuring vitamin D status and accurately reflects the free fractions of the vitamin D metabolites. Most authors consider vitamin D deficiency when serum/plasma 25(OH)D concentrations are less than 75 nmol/L or 30 ng/ml [7]. Obesity is linked to vitamin D deficiency since there is an inverse relationship between serum 25(OH)D and BMI larger than 30 kg/m2 [22]. The normal value of thyroid function was assessed as 0.3 mIU/L ≤ TSH ≤ 3.6 mIU/L. TSH levels more than 10 mIU/L and 3.6 mIU/L were used to diagnose

overt and subclinical hypothyroidism, respectively [18].

T4 levels in normal individuals were assessed to be between 4.5 and 12.0 g/dL. One of the distinct criteria for hypothyroidism cases was a T4 score less than 4.5. HT has been linked to vitamin D deficiency. Vitamin D deficiency was hypothesised to play a role in Hashimoto thyroiditis by resulting greater levels of autoantibody (TGAb). TPOAb and TGAb levels more than 40 and 100 IU/mL, respectively, were considered positive. The presence of high blood TPOAb or TGAb concentrations, as well as a decreased T4 value and an elevated TSH including subclinical and overt hypothyroidism patients, were used to diagnose Hashimoto thyroiditis [16, 24].

Vitamin D also induces T regulatory cells easier, which helps to reduce T cell-dependent immune reactions in autoimmune disorders. In genetically vulnerable population, T and B lymphocytes respond to thyroid antigens, resulting in HT.

Role of Vitamin D deficiency in Hashimoto's Thyroiditis:

Mechanism:

Hashimoto's thyroiditis (HT), also known as autoimmune or chronic lymphocytic thyroiditis, is one of the most common thyroid diseases, with a prevalence of 10–12% and increasing constantly. It is the most common thyroid disorder worldwide. HT is a critical autoimmune thyroid disorder that is characterised by T-cell infiltration and can lead to thyroid tissue loss [25]. It is 4-10 times more common in women than in men in the 30- 50 year old age group. The male-to-female ratio is approximately 7.2 [26]. Among various types of modifiers, gender, race, and age are all familiar HT modifiers, therefore white women between the ages of 45 and 55 are ten times more likely impacted than men by HT [27] . Furthermore, the etiopathogenesis of HT is influenced by environmental 30% and genetic 70%variables. Genetic factors mainly involves thyroid specific genes (Tg and TSHR), immune regulator genes (FOXP3, CTLA4, FRCL3, PTPN22, CD40 and CD25) and the primary histocompatibility gene known as HLA. Despite genetic factors, other parameters such as drugs, selenium, dietary iodine, pregnancy smoking, viral and bacterial infections, medicines and vitamin D deficiency are all potential environmental factors [26]. Among these mentioned biological risk factors, one of the main factor is vitamin D deficiency which responsible for HT disease. According to scientific investigations, vitamin D deficiency increases the serum of thyroid antibodies such as thyroglobulin (TGAb) and thyroid peroxidase antibodies (TPOAb) in human blood. Thyroid autoantibodies, in combination with thyroid ultrasonography, are diagnostic features and indicators for HT. Also, Serum antibodies interacting with TPO, TG, and an unidentified protein existed in colloid is seen in people with Hashimoto's thyroiditis [27-29]. The disease's clinical manifestations range from mild to severe hypothyroidism with or without goitre, as evidenced by the presence of one or both types of thyroid antibodies in euthyroid patients [30]. In accordance to current research, the key pathogenic features of HT include a Th1/Th2 cell imbalance and increased Th1 cell activity. Vitamin D deficiency may depress the immune system by suppressing numerous components of the HT immunological response. For instance,

1) Vitamin D binds to its receptor cells, preventing DC dependent T-cell activation, which lowers the generation of pro-inflammatory cytokines (TNF-α, IL-5, IL-17, IL-2), and thus reduce the immunological response mediated by these cytokines.
2) Vitamin D inhibits autoimmune thyroiditis by suppressing T-cell proliferation and inflammatory cytokine release by down regulating HLA-class-II-gene expression in the thyroid.

3) Vitamin D deficiency prompts a substantial number of B-cells to grow and develop into plasma cells, which subsequently secrete huge amounts of IgE, IgG, and other types of immunoglobulin's, causing thyroid cell destruction and triggering HT.
4) Vitamin D inhibits naive T-cell development into Th-17 cells and suppresses the release of Th-17 derived cytokines IL-21, IL-17 and while increasing T-reg cell metabolism to restore the body's Th-17/T-reg cell ratio and limit Th-17 cell caused thyroid inflammation [12, 31, 32].

Regardless, the pathological mechanism of vitamin D's role in the development of HT is still unknown.

Vitamin D Receptor and HT:

Vitamin D is known to have anti-inflammatory and immune-modulatory properties. The vitamin D nuclear receptor (VDR), which corresponds to the steroid immunoglobulin family and is extensively expressed in numerous cell types, particularly lymphocytes, macrophages, as well as several endocrine cells, is responsible for vitamin D's pleiotropic actions [16]. The VDR gene, which is found on chromosome 12q, has a lot of variation that affects how it works. TaqI in exon 9, FokI in exon 2, ApaI and BsmI in intron 8, and have been identified as four significant single nucleotide polymorphisms clustered in numerous haplotype blocks with considerable linkage disequilibrium.

There is high linkage disequilibrium between TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) and SNPs, but no considerable correlation disequilibrium with that of the FokI site. Certain VDR gene SNPs have been linked to a reduction in vitamin D function and have been linked to a variety of ailments, especially autoimmune disorders like Hashimoto thyroiditis. According to recent research paper, there is link between thyroid autoimmunity and vitamin D. (William et al 2021)

The FokI AA polymorphism was shown to be statistically greater in HT participants than in the control group (P value = 0.02), with a correspondingly higher serum 25-hydroxyvitamin D3 level (P value = 0.039). The difference in serum 25-OH-vitamin D3 levels between the HT and control groups was not statistically significant [33]. A Serbian study comprised 44 female Hashimoto's thyroiditis patients (mean age 38.4, SD 38.4) and 32 healthy geographically matched, sex-matched and age-matched with no personal history of endocrine or autoimmune disorders. Genomic DNA was extracted from peripheral blood using EDTA, and the targeted VDR gene was genotyped using the PCR-RFLP method after digestion with the restriction enzymes VDR-TaqI (rs731236), VDR-FokI (rs2228570) and VDR-ApaI (rs7975232). The present initial findings show a link between the VDR-FokI genetic polymorphisms and Hashimoto's thyroiditis in the Serbian community [34]. Wang and colleagues described Hashimoto's thyroiditis (HT) risk has been linked to four Vitamin D receptor gene polymorphisms including FokI, TaqI, BsmI and ApaI. Only the FokI polymorphism was found to be significantly linked to the risk of HT. Exclusively the Asian population had a substantial influence, according to subgroup analysis [35]. A total of 153 patients with various kinds of thyroid pathology were included in another study in western Ukraine. The 25-OH vitamin D levels in the serum of patients and healthy people were measured using the 25-OH vitamin D ELISA kit. In individuals with various kinds of thyroid pathology in the West-Ukrainian population, genotype variations of VDR rs2228570 were found to be no risk factors for lower serum 25-OH vitamin D or vitamin D insufficiency [36]. Egyptian subjects were contrasted to hypothyroid non-HT individuals in a cross-sectional study. Furthermore, even in patients expressing normal levels of vitamin D, patients with the FokI AA genotype have significantly greater amounts of 25-OH-vitamin

D3, indicating VDR malfunction [33]. In a case-control study, 100 clinically diagnosed HT patients (87 F, 13 M; average age SD 42, 15 years) and 100 healthy people were compared for BMI, age, sex, and blood sample month. In HT patients, vitamin D deficiency was shown to be significantly more prevalent than in the control group (70 vs 18.2 percent; p 0.0001). The VDR locus does not thought to play a role in establishing genetic susceptibility to the disease, at least within Caucasian people [37]. In a study of Iraqi people, dominant homozygous genotype (FF) was shown to be considerably higher in Hashimoto's thyroiditis patients than in the control group (P= 0.0002, OR= 2.22). Furthermore, results from the VDR-TaqI polymorphism revealed that people with the dominant homozygous TT-genotype or T-allele have a greater risk of getting Hashimoto's thyroiditis (OR= 2.64 and 1.78) [38]. An Iranian study included a number of 117 healthy controls and 121 AITDs adult clients in the same group were compared by sex and age. The frequencies of FokI and ApaI genotypes were not statistically different between the two groups. These findings imply that FokI polymorphisms play a role in AITD predisposition in the northwest Iranian population [39] According to Nashwa et al; vitamin D levels were shown to be lower in hypothyroid individuals than in control participants. TSH, anti-TG, anti-TPO, and HOMA-IR, levels were all inversely associated to vitamin D levels. In both the patient and control groups, the Vitamin D receptor polymorphism (Fok1 and Apa1) had no effect on TSH or vitamin D levels. Low vitamin D levels were linked to more modularity and vascularity and in the thyroid. This study found a link between vitamin D insufficiency and hypothyroidism, thyroid autoimmunity, enhanced thyroid gland volume, nodularity, and vascularity in hypothyroid patients [40].

Prevalence of Vitamin D Deficiency in Hashimato Disease:

One of the key etiological factors of HT is vitamin D deficiency, which is linked to illness severity. Egypt has a high prevalence rate of 25-hydroxyvitamin D3 deficiency, particularly among old men 19.3% and Egyptian children 11.5%. A case control research suggested that Vitamin D was deficient in 76.7% of Hashimoto thyroiditis and 70% of Graves' disease compared to 20.0% of healthy control [41]. Another study revealed that among HT cases, patients with overt hypothyroidism had a significantly higher prevalence of vitamin D insufficiency (60.4% vs. 44.1%, 21.7%, 37.1%, respectively, p <0.001) and lower 25(OH)D levels (80.1 ± 47.7 vs. 99.34 ± 61.2, 110.3 ± 69.9, 99.6 ± 53.7 nmol/L, respectively, p=0.009) compared with those with euthyroidism and subclinical hypothyroidism or those without AITD [42]. In one study, 72 percent of people with autoimmune thyroid dysfunction were vitamin D deficient, compared to slightly under 31 percent of people who were healthy. Similar, a study of Hashimoto's thyroiditis patients in Greece found that the more than 85% of them had lower vitamin D levels and increased concentrations of anti-thyroid antibodies [43]. Our research database review uncovered 56.5 % vitamin D deficiency high prevalence in HT participants

Data Summarized:

From each study, the data of concern was extracted by using excel sheet in random way. The list of extracted information was describe as: Author’s name and year, gender, age, season of sample collection, location, vitamin D detection method (assay method) , association of vitamin D with HT thyroiditis, control group number, HT group number, Bio mass index value and percentage of prevalence of HT patients in each study. In this systematic review, our database research consists of total 55 studies. Approximately 20 papers excluded due to

duplication and these papers are correlated with all autoimmune thyroid disorders such as graves' disease and subclinical hypothyroid patients. Authors reviewed 10 articles based on the abstract and titles. Finally, the current study deals with 25 full text assessed articles to summarize the data. Thus, a total of 25 up to date and current eligible research subjects focused on vitamin D deficiency in Hashimato disorder are included in this review. A flow sheet chart diagram briefly describes the study selection process in Figure 1.

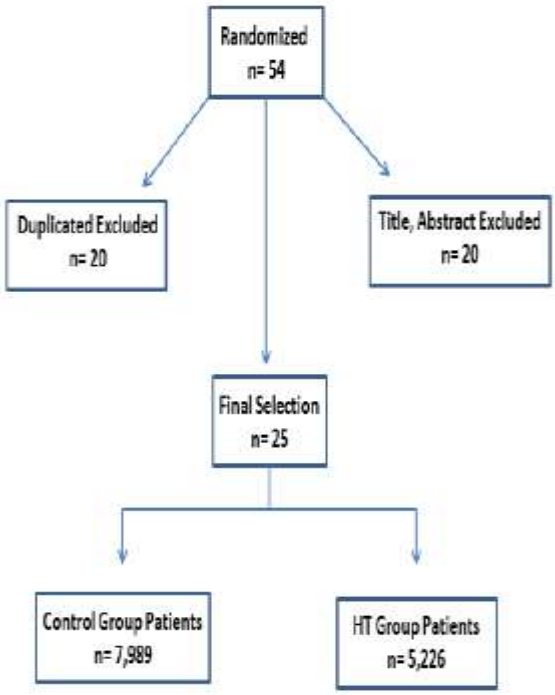

Figure 1: Consort diagram of selected studies

Overview of Included Database Subjects:

The up to date and current review states a total of 25 articles, including 6 cross sectional studies, 14 case control studies, 3 retrospective studies, 1 observational and 1 epidemiological study. The weight of sample articles varies in which total control group participants 7,989 and total Hashimato thyroiditis groups are 5,226. The articles included in present review were published between 2017 and 2021. Among these, 6 articles were from china [25, 44-47], 3 articles from Egypt [33, 41, 48], 3 each article from Georgia [49], Italy [37, 50], USA [51], 3 studies each from UK [52], Iraq [53], Bangladesh [54], 3 studies from Iran [55-57], 2 studies from Turkey [58, 59], 2 studies from Poland [60, 61], each study from Saudia Arabia [62] and 2 studies each from Brazil [63], and Spain [64]. Among these selected 25 studies, 15 studies report genders, 6 recruited only female, 2 enlisted only Male and 2 researches did not review gender type. A total of 25 samples pointed out the sample collection time of year. Furthermore, seventeen studies were described the body mass index (BMI) value. All incorporated studies well examined the deficiency of vitamin 25(OH) D and 25(OH) D3 in Hashimato diseased patients. None of them assessed the other autoimmune disease and supplementation of vitamin D in group's participants. Moreover, eighteen studies mentioned the positive association of vitamin d deficiency with HT disease and rest indicates negative association. The outline of characteristics of embodied studies is revealed in Table 1.

Table 1: Characteristics of HT based included studies

Authoryear	Location	Gender (F/M)	Age (year)	Season	BMI (kg/m^2)	Study design	Vitamin Assay method	P Value	Association	Ref
Hany William et al., 2021	Egypt	107/42	40	March 2018 to Oct. 2018	33.2	Cross - sectional	HPLC	<0.001	Positive	[33]
Fang et al., 2021	Tianjin, China	1812 M	45	2014	24.38	Epidemi-ological survey	ELISA	<0.001	Positive	[44]
Jing et al., 2021	China	35/15	38	Feb-Dec 2019	29.17	Cross - sectional	ELISA	<0.01	Positive	[45]
Salem et al., 2021	Egypt	240F	39	Autumn 2019 – 2020	-	Case control	ELISA	<0.001	Positive	[48]
Nino et al., 2021	Georgia	1097/198	45	Mid spring 2018 - 2019	-	Retrospec tive	CLIA	0.002	Positive for female	[49]
Maja et al., 2021	Italy	637 F	38	2015-2017 all season	23.52	Retrospec tive	CLIA	0.005	Negative	[50]
Rola et al., 2021	CA,USA	98 F	50	2018 - 2019	18.5	Observati onal	LC-MS/MS	0.028	Negative	[51]
Iryna et al., 2021	UK	153	30	Sep 2017 – Dece 2020	-	Case control	ELISA	0.006	Moderate positive	[52]
Izzat et al., 2021	Iraq	24/12	40	Dec 2018 – April 2019	-	Case control	ECLA	<0.001	Positive	[53]
Chao et al., 2020	China	3163 M	48	January 2018 - Dec. 2018	24.37	Cross - sectional	CLIA	<0.001	Negative	[25]
Nazma et al., 2020	Banglade sh	178/117	42	January 2019 to March 2020	26.84	Cross - sectional	Vitros ECI	<0.001	Positive	[54]
Sergio et al., 2021	Spain	200	48	Feb. 2018 - March 2019	-	Case control	ECLA	0.01	Positive	[64]
Robert et al., 2019	Poland	75 F	45	Jan-Aug 2016	35	Case control	CLIA	0.05	Positive	[60]
Botelho et al., 2018	Brazil	143/15	46.8	Jan-Dec 2016	28.1	Case control	CLIA	0.191	Negative	[63]
Xiang et al., 2018	China	36/158	49.4	16 Mar. 2014- 24 Feb. 2017	24.2	Case control	ICMA	<0.001	Positive	[46]
Robert et al., 2018	Poland	57 F	50	Jan-Aug 2016	-	Case control	CLIA	<0.01	Positive	[61]
Solhjoo et al., 2018	Iran	50/30	39.4	April - August 2016.	-	Cross - sectional	ECLA	<0.001	Positive	[55]
Abbas et al., 2018	Saudia Arabia	50 F	30	Sep 2015-Noov 2016	29.9	Cross - sectional	ICMA	0.89	Negative	[62]
Yurekli et al., 2018	Turkey	87/9	45.1	Oct, Nov 2016	29.7	Case control	CLIA	0.482	Negative	[58]
Bakr et al., 2017	Egypt	20/10	40	June 2017	-	Case control	CLIA	<0.001	Positive	[41]
Wencaiet al., 2017	China	31/26	42.41	Nov 2015, Janua 2016	23.01	Case control	ELISA	<0.05	Positive	[47]
Salvatri et al., 2017	Italy	175/25	42	Autumn to Spring	27	Case control	ECLIA	<0.05	Positive	[37]
Anaraki et al., 2017	Iran	59/6	44.1	Feb to July 2015	26.9	RCT	CLIA	<0.05	Negative	[56]
Nalbant et al., 2017	Turkey	88/5	36	April to December 2010	27.3	Case control	ECLA	0.001	Positive	[59]
Amir et al., 2017	Iran	16/89	38	Augest to Oct 2016	26	Case control	ECLIA	0.01	Positive	[57]

Table 2: Twenty-five- OH – vitamin D deficiency among HT studied groups

Authors Name	Control group n= 734	Patients with HT n=2,201	Control group 25(OH)D	HT group 25(OH) D	HT (%)
Hany William et al 2021	48	112	37.5	51.7	93.8
Fang et al 2021	237	1575	45.63	49.86	7.7
Salem et al 2021	120	120	19.0	7.9	68.3
Yurekli et al 2018	29	67	54.1	53.1	47.8
Wencaiet al 2017	51	63	83.49	45.77	70.3
Salvatori et al 2017	100	100	35.7	21.2	70
Nalbant et al 2017	34	59	10.67	13.27	63.4
Amir et al 2017	105	105	39.81	32.22	40

Findings from Association of Serum 25 (OH) D deficiencies with HT:

There is no exact definition of vitamin D deficiency in previous studies. Most studies defined that the cut off level of serum 25(OH)D less than 20 ng/mL concentration [65]. Some studies defined less than 15 ng/mL [66] or other 10 ng/mL [63, 67]. All above mentioned studies reviewed higher value of prevalence of vitamin D deficiency. The current systematic review comprised of 4322 participants who demonstrated prevalence of vitamin D deficiency in Hashimato patients. Our research database review disclosed 56.5 % vitamin D deficiency high prevalence in HT participants (Figure 2). Despite the fact that the clear mechanism of vitamin D deficiency with Hashimato disease was under debate, still effort continued to find the association of vitamin d deficiency with Hashimato disease. The different variable inspections were carried for region, gender type, age, body mass index, study biomarkers and serum 25 (OH) D concentrations. Our results describe the mean age value of 41.63 years of HT patients with vitamin D deficiency. The association of mean value of 25(OH) D with HT patients was shown in Table 2.

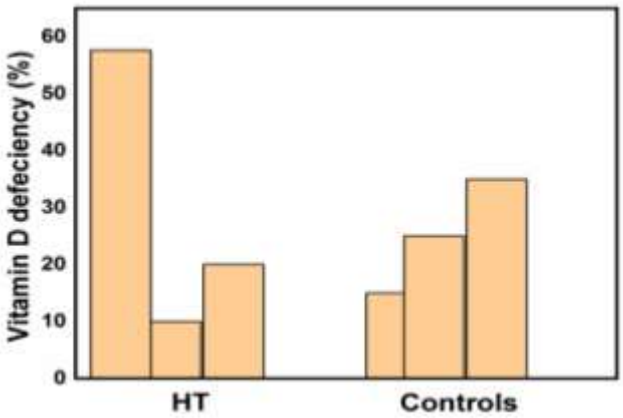

Figure 2: 25 (OH) D deficiency in HT and Controls

DISCUSSION:

Our findings report a positive association between serum 25 (OH) D deficiencies and HT disease however, the causes and physiological mechanism remain unclear. Plenty of studies also revealed the higher prevalence of vitamin D deficiency in Hashimoto autoimmune patients as compared to control group patients. Similarly, Evliyaoğlu et al. Investigated the significant higher prevalence (71.1%) of vitamin d deficiency in Hashimoto's patient's adolescents relative to control group with 51.9 % prevalence at 0.025 p-value He observed that Hashimoto disease was 2.28 times greater in individual patients with deficiency levels less than 20 ng/mL [68]. Another Spanish study suggests that mean value of twenty-five Hydroxy (16.8 ± 9.3) was recognized lower in Hashimoto patients with respect to control (24.1 ± 9.4 ng/mL) with p-value less than 0.01 respectively. The frequency twenty-five Hydroxy vitamin D was found to be 76 times and 35% in HT patients having p- value less than 0.001 [69]. Furthermore, an Iranian case control study was carried out to evaluate the status of vitamin D deficiency in Hashimato hypothyroidism. The consequences revealed that serum level of 25(OH) D was lower in HT patients and inverse relationship find out between thyroid antibodies TGAb and vitamin D

concentration. Author also observed the positive correlation between thyroid stimulating hormone and vitamin D level in HT patients with p-value 0.008 respectively [16]. Sandeep et al. demonstrated the association of low vitamin D level in HT participants by using national health surveys. The statistical analyses showed that almost 25.6% HT patients had low level of vitamin D relative to control one about 20.6 %. Authors also observed that odd ratio of HT participants was relatively higher with vitamin D deficiency [70]. The case control research examined the low level of 25-hydroxy vitamin D in HT participants relative to control participants. Author identified inverse relation between TGAb and serum vitamin D. whereas, a direct association of TSH and vitamin D in HT was find out [16]. Jamka et al. probably described the severity of HT with low vitamin D concentration. A negative association between thyroid antibodies and vitamin D level was detected [71]. It was observed that our findings were well matched with above mentioned studies. Our research data base review revealed 56.5 % vitamin D deficiency high prevalence in HT participants with p value less than 0.001 as compared to control group. However, other factors including genetic polymorphism and vitamin D receptor cells increase the concentration of thyroid antibodies and leads to vitamin D deficiency in Hashimoto thyroiditis. Mazokopakis et al. reported the effect of genetic polymorphism in vitamin D deficiency correlation with HT antibodies. He investigated that an immunologic reaction in HT patients was initiated when thyrocytes cells assert MHC degree two surface HLA/DR antigens, a system elicited by the generation from lymphocytes Th1 helper cell of inflammatory specifically IFN-γ Cytokines hindered by 25[OH]D may bias to the expansion of HT [72]. Other immunological factors such as mean age mean BMI of the studied populations were also attained. It should be noted that, level of serum 25(OH) D may be varies by smoking, gender and age as well [73-75]. The low concentration of 25(OH) D has been also examined in fat children and in overweight grown-up participants of both genders, especially for compatriots dwelling in advanced nations [76-78]. The association between body mass index and vitamin D level is sophisticated, potentially two dimensional, and maybe encompasses separateness of vitamin in adipose tissue, various lifestyle positions, patterns of diet and volumetric dilution [79]. Discrepancies in Body mass index have also been correlated with distinctions in age of participant, thyroid functions, educational achievements, health care assistance and age, which may involve or negotiate high mean BMI value in HT patients [80, 81]. However, the variables fluctuated considerably between our selected studies, and making the difficult interpretation of this subject literature. Moreover, the mean size effect become increasingly problematic in the existence of modifiers, designation of autonomous predictors, which might instruct the layout of future trials [82]. The advantage of our review is that we collect up to date and current studies based on association between vitamin D deficiency and HT. We observed high prevalence of vitamin D deficiency in HT patients as well as. Overall vitamin D deficiency causes dysfunction of thyroid hormone by increasing the thyroid antibodies.

The drawbacks of this study are there was substantial heterogeneity in our review that affected the generalisation of consequences. Factors such as BMI, age difference, study type, season, location, and vitamin D detection method might be the sources of heterogeneity. However there was no exact mechanism of association between vitamin D deficiency and HT.

CONCLUSION:

In the current systematic study, a significantly low serum level of vitamin D in HT patients was identified relative to healthy population. We identified high prevalence of vitamin D deficiency in HT patients rather than none HT patients. Furthermore, we analysed the various parameters including age distribution, gender, sample size, study design, BMI, vitamin-D assay route, and mean difference value of vitamin D deficiency in HT and non HT patients. However, well-developed prospective studies need to be designed and clinical trials are necessary for a deeper insight of the association between low level of vitamin D and Hashimoto thyroiditis.

REFERENCES:

1) Borradale, D. and M. Kimlin, Vitamin D in health and disease: an insight into traditional functions and new roles for the 'sunshine vitamin'. Nutrition research reviews, 2009. **22**(2): p. 118-136.
2) Holick, M.F., Photobiology of vitamin D, in vitamin D. 2018, Elsevier. p. 45-55.
3) Máčová, L. and M. Bičíková, Vitamin D: Current Challenges between the Laboratory and Clinical Practice. Nutrients, 2021. **13**(6): p. 1758.
4) Vatandost, S., et al., Prevalence of vitamin D deficiency in Iran: a systematic review and meta-analysis. Nutrition and health, 2018. **24**(4): p. 269-278.
5) Skaaby, T., et al., Prospective population-based study of the association between vitamin D status and incidence of autoimmune disease. Endocrine, 2015. **50**(1): p. 231-238.
6) Mendes, M., et al., Future perspectives in addressing the global issue of vitamin D deficiency. Proceedings of the Nutrition Society, 2020. **79**(2): p. 246-251.
7) Amrein, K., et al., Vitamin D deficiency 2.0: an update on the current status worldwide. European journal of clinical nutrition, 2020. **74**(11): p. 1498-1513.
8) Hassan-Smith, Z.K., M. Hewison, and N.J. Gittoes, Effect of vitamin D deficiency in developed countries. British medical bulletin, 2017. **122**(1): p. 79-89.
9) Nimitphong, H. and M.F. Holick, Vitamin D status and sun exposure in Southeast Asia. Dermato-endocrinology, 2013. **5**(1): p. 34-37.
10) Arabi, A., R. El Rassi, and G.E.-H. Fuleihan, Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. Nature Reviews Endocrinology, 2010. **6**(10): p. 550-561.
11) Berridge, M.J., Vitamin D deficiency and diabetes. Biochemical Journal, 2017. **474**(8): p. 1321-1332.
12) Zhao, R., et al., Immunomodulatory Function of Vitamin D and Its Role in Autoimmune Thyroid Disease. Frontiers in Immunology, 2021. **12**: p. 352.
13) Shahid, M.A., M.A. Ashraf, and S. Sharma, Physiology, thyroid hormone. 2018.
14) Teixeira, P.d.F.d.S., P.B. Dos Santos, and C.C. Pazos-Moura, The role of thyroid hormone in metabolism and metabolic syndrome. Therapeutic advances in endocrinology and metabolism, 2020. **11**: p. 2042018820917869.
15) He, J., et al., The Relationship Between Thyroid Function and Metabolic Syndrome and Its Components: A Cross-Sectional Study in a Chinese Population. Frontiers in Endocrinology, 2021. **12**: p. 314.
16) Ahi, S., M.R. Dehdar, and N. Hatami, Vitamin D deficiency in non-autoimmune hypothyroidism: a case-control study. BMC endocrine disorders, 2020. **20**(1): p. 1-6.
17) Pittas, A., B. Dawson-Hughes, and M. Staten, Vitamin D Supplementation and Prevention of Type 2 Diabetes. Reply. The New England journal of medicine, 2019. **381**(18): p. 1785-1786.

18) Grant, W.B. and B.J. Boucher, Why secondary analyses in vitamin d clinical trials are important and how to improve vitamin d clinical trial outcome analyses—a comment on "Extra-Skeletal Effects of Vitamin D, Nutrients 2019, 11, 1460". Nutrients, 2019. **11**(9): p. 2182.
19) Nettore, I.C., et al., Sunshine vitamin and thyroid. Reviews in Endocrine and Metabolic Disorders, 2017. **18**(3): p. 347-354.
20) Kim, D., The role of vitamin D in thyroid diseases. International journal of molecular sciences, 2017. **18**(9): p. 1949.
21) Kivity, S., et al., Thyroid disease and vitamin D deficiency. Annals of the Rheumatic Diseases, 2010. **69**(Suppl 2): p. A62-A62.
22) Nair, R. and A. Maseeh, Vitamin D: The "sunshine" vitamin. Journal of pharmacology & pharmacotherapeutics, 2012. **3**(2): p. 118.
23) Choi, Y.M., et al., Low levels of serum vitamin D3 are associated with autoimmune thyroid disease in pre-menopausal women. Thyroid, 2014. **24**(4): p. 655-661.
24) Aminorroaya, A., et al., Incidence of thyroid dysfunction in an Iranian adult population: the predictor role of thyroid autoantibodies: results from a prospective population-based cohort study. European journal of medical research, 2017. **22**(1): p. 1-10.
25) Chao, G., Y. Zhu, and L. Fang, Correlation Between Hashimoto's Thyroiditis–Related Thyroid Hormone Levels and 25-Hydroxyvitamin D. Frontiers in endocrinology, 2020. **11**: p. 4.
26) Chiovato, L., F. Magri, and A. Carlé, Hypothyroidism in context: where we've been and where we're going. Advances in therapy, 2019. **36**(2): p. 47-58.
27) Merrill, S.J. and Y. Mu, Thyroid autoimmunity as a window to autoimmunity: an explanation for sex differences in the prevalence of thyroid autoimmunity. Journal of theoretical biology, 2015. **375**: p. 95-100.
28) Caturegli, P., A. De Remigis, and N. Rose, Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmunity reviews, 2014. **13**(4-5): p. 391-397.
29) Kolypetri, P., et al., Genes and environment as predisposing factors in autoimmunity: acceleration of spontaneous thyroiditis by dietary iodide in NOD. H2h4 mice. International reviews of immunology, 2015. **34**(6): p. 542-556.
30) Akamizu, T. and N. Amino, Hashimoto's thyroiditis. Endotext [Internet], 2017.
31) Chahardoli, R., et al., Can supplementation with vitamin D modify thyroid autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and thyroid profile (T3, T4, TSH) in Hashimoto's thyroiditis? A double blind, Randomized clinical trial. Hormone and Metabolic Research, 2019. **51**(05): p. 296-301.
32) Krysiak, R., W. Szkróbka, and B. Okopień, The effect of vitamin D on thyroid autoimmunity in levothyroxine-treated women with Hashimoto's thyroiditis and normal vitamin D status. Experimental and Clinical Endocrinology & Diabetes, 2017. **125**(04): p. 229-233.
33) Hanna, H.W.Z., et al., Vitamin D status in Hashimoto's thyroiditis and its association with vitamin D receptor genetic variants. The Journal of Steroid Biochemistry and Molecular Biology, 2021. **212**: p. 105922.
34) Djurovic, J., et al., Association between FokI, ApaI and TaqI RFLP polymorphisms in VDR gene and H ashimoto's thyroiditis: preliminary data from female patients in S erbia. International Journal of Immunogenetics, 2015. **42**(3): p. 190-194.
35) Wang, X., et al., Vitamin D receptor gene FokI but not TaqI, ApaI, BsmI polymorphism is associated with Hashimoto's thyroiditis: a

meta-analysis. Scientific reports, 2017. **7**(1): p. 1-11.
36) Kamyshna, I.I., et al., 25-OH Vitamin D blood serum linkage with VDR gene polymorphism (rs2228570) in thyroid pathology patients in the West-Ukrainian population. Journal of Medicine and Life, 2021. **14**(4): p. 549.
37) Giovinazzo, S., et al., Vitamin D receptor gene polymorphisms/haplotypes and serum 25 (OH) D 3 levels in Hashimoto's thyroiditis. Endocrine, 2017. **55**(2): p. 599-606.
38) Majid, W.J., A.H.A. Algenabi, and A.A. Alwadees, Vitamin-D Receptor (VDR) Gene Polymorphisms (FokI and TaqI) in Patients with Hashimoto's Thyroiditis of Iraqi Population. European Journal of Molecular & Clinical Medicine, 2020. **7**(2): p. 64-68.
39) Zarrin, R., et al., The association of FokI and ApaI polymorphisms in vitamin D receptor gene with autoimmune thyroid diseases in the northwest of Iran. Medical journal of the Islamic Republic of Iran, 2018. **32**: p. 4.
40) ElRawi, H.A., et al., Study of Vitamin D level and Vitamin D receptor polymorphism in hypothyroid Egyptian patients. Journal of thyroid research, 2019. **2019**.
41) Bakr, H.G. and T.E. Meawed, Relevance of 25 (OH) Vitamin D deficiency on Hashimoto's Thyroiditis. The Egyptian journal of immunology, 2017. **24**(2): p. 53-62.
42) Kim, D., Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis. Hormones, 2016. **15**(3): p. 385-393.
43) Mazokopakis, E.E., et al., Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis. Hell J Nucl Med, 2015. **18**(3): p. 222-7.
44) Fang, F., et al., Vitamin D deficiency is associated with thyroid autoimmunity: results from an epidemiological survey in Tianjin, China. Endocrine, 2021: p. 1-8.
45) Salem, T.M., E. Abdelmonem, and A. Fayad, Hashimoto's thyroiditis, iron, and vitamin D deficiency among Egyptian female patients: associations and possible causalities. Hormones, 2021: p. 1-4.
46) Xu, J., et al., Low vitamin D levels are associated with cognitive impairment in patients with Hashimoto thyroiditis. BMC endocrine disorders, 2018. **18**(1): p. 1-6.
47) Ke, W., et al., 25-Hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. Endocrine journal, 2017. **64**(6): p. 581-587.
48) He, J., et al., Correlation between serum 25-(OH) D 3 level and immune imbalance of Th1/Th2 cytokines in patients with Hashimoto's thyroiditis and its effect on autophagy of human Hashimoto thyroid cells. Experimental and Therapeutic Medicine, 2021. **21**(5): p. 1-8.
49) Turashvili, N., L. Javashvili, and E. Giorgadze, Vitamin D Deficiency Is More Common in Women with Autoimmune Thyroiditis: A Retrospective Study. International journal of endocrinology, 2021. **2021**.
50) Cvek, M., et al., Vitamin D and Hashimoto's Thyroiditis: Observations from CROHT Biobank. Nutrients, 2021. **13**(8): p. 2793.
51) Rola, R., et al., Application of Dried Blood Spots and Serum Samples for the Determination of Vitamin D Metabolites in the Group of Healthy Women and with Hashimoto's Thyroiditis. Chromatographia, 2021: p. 1-7.
52) Kamyshna, I., L. Pavlovych, and A. Kamyshnyi, Association between Serum Brain-derived Neurotrophic Factor and 25-OH Vitamin D Levels with Vitamin D Receptors Gene Polymorphism (rs2228570) in Patients with Autoimmune Thyroiditis and Hypothyroidism. Open Access Macedonian Journal of Medical Sciences, 2021. **9**(A): p. 659-664.
53) AlRayahi, I.A.M., R.H. Sanyi, and S.A. AlAsadi, Hypovitaminosis D in Iraqi Hashimoto Thyroiditis Patients. Annals of the Romanian

Society for Cell Biology, 2021. **25**(6): p. 8218-8222.

54) Akter, N. and T. Akter, Pattern of Vitamin D deficiency in Hashimoto's thyroiditis and its association with thyroid hormone. Thyroid Research and Practice, 2020. **17**(3): p. 141.

55) Solhjoo, M., et al., The Prevalence of Vitamin D Deficiency in Patients with Hashimoto's Hypothyroidism. MJ Immu, 2018. **2**(1): p. 006.

56) VAHABI, A.P., et al., EFFECTS OF VITAMIN D DEFICIENCY TREATMENT ON METABOLIC MARKERS IN HASHIMOTO THYROIDITIS PATIENTS. 2016.

57) Faghfouri, A.H., et al., ASSOCIATION OF VITAMIN D STATUS AND BSMI POLYMORPHISM IN VITAMIN D RECEPTOR GENE WITH HASHIMOTO DISEASE IN URMIA. Studies in Medical Sciences, 2017. **28**(9): p. 572-581.

58) Yurekli, B.S., et al., Assessment of vitamin D level in Hashimoto thyroiditis in Turkish population. Medicine, 2019. **8**(1): p. 109-12.

59) Nalbant, A., et al., Association of vitamin D insufficiency/deficiency with thyroid artery Doppler ultrasonography in patients with Hashimoto thyroiditis. Pakistan journal of medical sciences, 2017. **33**(2): p. 295.

60) Krysiak, R., K. Kowalcze, and B. Okopień, Selenomethionine potentiates the impact of vitamin D on thyroid autoimmunity in euthyroid women with Hashimoto's thyroiditis and low vitamin D status. Pharmacological Reports, 2019. **71**(2): p. 367-373.

61) Krysiak, R., W. Szkróbka, and B. Okopień, Moderate-dose simvastatin therapy potentiates the effect of vitamin D on thyroid autoimmunity in levothyroxine-treated women with Hashimoto's thyroiditis and vitamin D insufficiency. Pharmacological Reports, 2018. **70**(1): p. 93-97.

62) Aljahdali, B.A., VITAMIN D STATUS AND AUTOIMMUNE DISEASE (HASHIMOTO'S THYROIDITIS) IN SAUDI ARABIAN WOMEN. 2018.

63) Botelho, I.M.B., et al., Vitamin D in Hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status. Endocrine journal, 2018. **65**(10): p. 1029-1037.

64) Roman, G.S., et al. Vitamin D deficiency and Hashimoto's thyroiditis. in Endocrine Abstracts. 2021. Bioscientifica.

65) Pilz, S., et al., Rationale and plan for vitamin D food fortification: a review and guidance paper. Frontiers in endocrinology, 2018. **9**: p. 373.

66) Saini, V., et al., A preliminary evaluation of interrater reliability and concurrent validity of open-ended indirect assessment. Behavior analysis in practice, 2020. **13**(1): p. 114-125.

67) Štefanić, M. and S. Tokić, Serum 25-hydoxyvitamin D concentrations in relation to Hashimoto's thyroiditis: a systematic review, meta-analysis and meta-regression of observational studies. European journal of nutrition, 2020. **59**(3): p. 859-872.

68) Evliyaoğlu, O., et al., Vitamin D deficiency and Hashimoto's thyroiditis in children and adolescents: A critical vitamin D level for this association? Journal of clinical research in pediatric endocrinology, 2015. **7**(2): p. 128.

69) Sönmezgöz, E., et al., Hypovitaminosis D in Children with Hashimoto s Thyroiditis. Revista medica de Chile, 2016. **144**(5): p. 611-616.

70) Appunni, S., et al., Association between vitamin D deficiency and hypothyroidism: results from the National Health and Nutrition Examination Survey (NHANES) 2007–2012. BMC Endocrine Disorders, 2021. **21**(1): p. 1-9.

71) Jamka, M., M. Ruchała, and J. Walkowiak, Vitamin D and Hashimoto's disease. Polski merkuriusz lekarski: organ Polskiego

Towarzystwa Lekarskiego, 2019. **47**(279): p. 111-113.

72) Mazokopakis, E.E. and D.A. Kotsiris, Hashimoto's autoimmune thyroiditis and vitamin D deficiency. Current aspects. Hellenic journal of nuclear medicine, 2014. **17**(1): p. 37-40.

73) Edwards, M., et al., The global epidemiology of vitamin D status. J Aging Res Clin Prac, 2014. **3**(3): p. 148-58.

74) Ovesen, L., R. Andersen, and J. Jakobsen, Geographical differences in vitamin D status, with particular reference to European countries. Proceedings of the Nutrition Society, 2003. **62**(4): p. 813-821.

75) Johnson, L., et al., Impact of gender on vitamin D deficiency in morbidly obese patients: a cross-sectional study. European journal of clinical nutrition, 2012. **66**(1): p. 83-90.

76) Poomthavorn, P., et al., Vitamin D status and glucose homeostasis in obese children and adolescents living in the tropics. International journal of obesity, 2012. **36**(4): p. 491-495.

77) Saneei, P., A. Salehi-Abargouei, and A. Esmaillzadeh, Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. Obesity Reviews, 2013. **14**(5): p. 393-404.

78) Katznelson, L., et al., Acromegaly: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism, 2014. **99**(11): p. 3933-3951.

79) Pourshahidi, L.K., Vitamin D and obesity: current perspectives and future directions. Proceedings of the Nutrition Society, 2015. **74**(2): p. 115-124.

80) Knudsen, N., et al., Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. The Journal of Clinical Endocrinology & Metabolism, 2005. **90**(7): p. 4019-4024.

81) Bhaskaran, K., et al., Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3· 6 million adults in the UK. The lancet Diabetes & endocrinology, 2018. **6**(12): p. 944-953.

82) Ewing, C., 'Color Him Black': Erotic Representations and the Politics of Race in West German Homosexual Magazines, 1949-1974. Sexuality & Culture, 2017. **21**(2).