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Review

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Vitamin D and Carotid Intima Media Thickness: A valuable association or another one-hit wonder?

Witamina D i grubość warstwy środkowej tętnicy szyjnej: wartościowy związek czy hit jednego sezonu?

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Summary

Atherosclerosis is a chronic inflammatory process that leads to narrowing of the arteries due to the accumulation of plaque on the walls of the arteries. Carotid Intima Media Thickness (CIMT) is a marker which provides valuable information on the risk of atherosclerosis. It is an inexpensive tool to monitor arrest, progression or regression of the plaque formation. Vitamin D concentration, despite crucial role and pleiotropic activity of the micronutrient, is often grossly insufficient. The association between vitamin D deficiency and CIMT development has been indicated in multiple research studies. The aim of this study was to collect literature data describing the relationship between 25-hydroxyvitamin D concentration and CIMT evolution in various diseases. Original articles for the preparation of this manuscript were extracted from PubMed and Cochrane databases. After careful consideration, 44 original papers from the initial number of 64 articles were included in the analysis. Articles classified as randomized clinical trials, cross-sectional studies, case control studies and cohort studies We observed numerous contradictions in collected results. These contradicting results may be caused by comparing articles that very often are related to populations with different baseline characteristics of the studied populations. Incoherent results have led to the conclusion that further research is required to assess the association between analyzed factors.

Keywords: carotid stenosis • carotid intima media thickness • vitamin D • 25-hydroxyvitamin D

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Abbreviations: **1α,25(OH)2D** – 1α,25-dihydroxyvitamin D; **25(OH)D)** – 25-hydroxyvitamin D; **BD** – Behçet's disease; **BMI** – Body Mass Index; **B-PROOF study** – B-Vitamins for the Prevention Of Osteoporotic Fractures study; **Ca** – calcium; **Ca^{2+}** – calcium ions; **CCA** – common carotid artery; **CCA-IMT** – common carotid artery intima-media thickness; **CIMT** – carotid intima media thickness; **CIMT SDS** – carotid intima-media thickness standard deviation score; **CKD** – chronic kidney disease; **CS** – carotid stenosis; **CVD** – cardiovascular disease; **DHCR7 –** 7-dehydrocholesterol reductase; **HbA1c** – glycated haemoglobin; **HDL** – high density lipoprotein; **HIV** – human immunodeficiency virus; **ICA-IMT** – internal carotid artery intima-media thickness; **IFG** – impaired fasting glucose; **IGT** – impaired glucose tolerance; **IMPROVE** – longitudinal Carotid Intima Media Thickness and IMT – Progression as Predictors of Vascular Events in a High Risk European Population; **IMT** – intima-media thickness; **K** – potassium; **KORA study** – Cooperative Health Research in the Region of Augsburg; **LAPS** – Lupus Atherosclerosis Prevention Study; **MIMT** – maximum intima-media thickness; **MS** – metabolic syndrome; **NRTIs** – nucleoside reverse transcriptase inhibitors; **OCp** – mild osteoarthritic; **PAD** – peripheral arterial disease; **PHPT** – primary hyperparathyroidism; **PIs** – protease inhibitor; **pSoBid** – Psychological, social and biological determinants of ill health study; **pSS** – primary Sjögren's Syndrome; **PTH** – parathyroid hormone; **RA** – rheumatoid arthritis; **ROS** – reactive oxygen species; **TG** – triglycerides; **USG Doppler** – Doppler ultrasonography; **VDR** – vitamin D receptor.

INTRODUCTION

Vitamin D is a chemical compound with steroid structure, which is converted in humans into intermediate form 25-hydroxyvitamin D [25(OH)D)] and finally into the active form of 1α,25-dihydroxyvitamin D [1α,25$(OH)_2$D] [34]. The active form of vitamin D interacts with the vitamin D receptor (VDR), present in most tissues, which is a transcription factor that regulates the expression of many genes [14]. The concentration of vitamin D depends both on its synthesis, mainly in keratinocytes from 7-dehydrocholesterol after sun exposure, and the external delivery of this vitamin with food [6]. According to current standards, it is assumed that we are dealing with a deficiency of vitamin D in people with a concentration of 25(OH)D <50nmol/L (<20 ng/ml). The state of lowering vitamin D concentration occurs when the 25(OH)D concentration value is between 50–75 nmol/L (20-30 ng/ml), whereas >75 nmol/L (>30 ng/ml) is considered to be the optimal concentration [27, 49]. It should be noted that the concentration of vitamin D to a large extend also depends on the skin pigmentation, the quality of food consumed, time and intensity of solar radiation, age, use of sunscreen and sun exposure behavior [42]. Vitamin D has a pleiotropic activity in normal concentrations, plays a key role in the calcium-phosphate administration, which is the main function of this vitamin [19, 35]. However, this is not its only activity. It also has a number of other properties; for example, the appropriate concentration of vitamin D regulates the immune response of our body, inhibits inflammatory processes and has a beneficial effect on the nervous system [6, 51, 61]. The state associated with vitamin D deficiency negatively affects the circulatory system of our body. Cardiovascular diseases such as myocardial infarction or hypertension are associated with vitamin D deficiency and with the disruption of Ca^{2+} or reactive oxygen species (ROS) signaling systems, which require the correct concentration of the active form of vitamin D for proper functioning [40]. The appropriate concentration of vitamin D works positively on the cardiovascular system, reducing blood pressure, preventing plaque formation and the development of inflammation within the formation of atherosclerotic plaque in the blood vessels [48].

Atherosclerosis is a chronic inflammatory process that is located in the aorta and medium-sized arteries. As a result of plaque deposition and physical forces associated with blood flow, intravascular coagulation occurs and causes the closure of the vessel's lumen and sudden suppression of blood flow in the artery (coronary heart disease, infarction, stroke) [21]. Carotid stenosis (CS) involves the narrowing of major arteries that supply the brain with oxygenated blood (common carotid artery; CCA). Narrowing of the carotid arteries is caused by the accumulation of atherosclerotic plaque in the arterial wall, which results in reduced blood flow to the brain [17, 30]. Doppler ultrasonography (USG Doppler) in cardiology is a non-invasive vascular imaging method that has become a valuable technique for detecting and monitoring adverse structural changes in arterial vessels. Essentially, this method allows us to detect vessel changes before the appearance of disease symptoms [39]. Assessment of the intima-media thickness (IMT) is widely used. Published studies show that IMT may be associated with the development of atherosclerosis, which is why it is considered to be an important cardiovascular risk factor [15, 52]. A value not exceeding 0.9 mm is considered a normative value of IMT. The thickness of the arterial wall defined in this way is treated as a determinant of the initial stage of the atherosclerotic process [38].

The purpose of the following study was to collect literature data describing the relationship between 25-hydroxyvitamin D concentration and the presence of intima-media changes in various diseases.

MATERIAL AND METHODS

Search strategy and data sources

Articles for the preparation of this manuscript were extracted by searching for literature in PubMed and Cochrane databases. This review was limited to original, published articles concerning the concentration of vitamin D and the development of CS in various diseases. The search strategy was presented in Fig.1. Articles published until 18 January 2018 were selected for the analysis, as this is the time when electronic databases were searched. The analysis included both research on adults and children. Publications related to animal experiments, focused on drug testing, written in a different language than English were excluded.

Study selection and data extraction

Three co-authors of the article evaluated the publications independently of each other. Articles classified as meta-analysis, letter to editor, invited commentary, review article and systematic review were rejected. Articles that qualified for further analysis concerned scientific studies such as the following: randomized clinical trials, cross-sectional studies, case control studies and cohort studies. The search strategy was presented in Fig. 2. Article qualification was performed by two authors of the presented study. The articles obtained information on the size of the study group, IMT, vitamin D concentration and baseline characteristic.

RESULTS

Articles that met our inclusion criteria were divided depending on the disease entities of the analyzed patients (Table 1). Concentration units of 25(OH)D vitamin has been converted to nmol/L with use of ENDMEMO Vitamin D (25-Hydroxyvitamin D) Unit Conversion tool: http://www.endmemo.com/medical/unitconvert/Vitamin_D.php.

Vitamin D and Carotid IMT in groups of healthy people

Among all the papers qualified for this analysis, 10 original articles concerned the relationship between vitamin D concentration and the value of IMT among various groups of healthy people without chronic diseases. Part of the studies concerning middle-aged and elderly participants indicates the lack of dependence between vitamin D concentration and IMT progression. In the research involving healthy subjects with elevated homocysteine level (12–50 μmol/l) a non-linear association between 25(OH)D and pre-clinical stages of cardiovascular disease was observed. Higher concentration of serum 25(OH)D was associated with higher values of carotid artery intima-media thickness (CIMT) in vitamin D sufficient research participants [58]. However, the concentration of vitamin D in this population was of a lower level, but there was no clear deficiency. Also, no independent relationship between serum 25(OH) D concentration and Common Carotid Artery Intima-media thickness (CCA-IMT), Internal Carotid Artery Intima-media thickness (ICA-IMT) was observed in 3.251 patients with mean age of 64 years. Statistical analysis shows no influence of 25(OH)D concentration on the development of CIMT and atherosclerosis in elderly healthy patients [7]. The drawback of the mentioned study is the lack of vitamin D values; therefore, there was no possibility to assess if it was in vitamin D deficient population or population with optimal concentrations. Similarly, the lack of correlation between vitamin D concentration and CIMT value was indicated by studies based on the results of a group of aged 35–64 subjects who lived at the extremes of the socioeconomic spectrum (the level of vitamin D is unknown) or in a small group of children with mean age of 13.7 with near optimal vitamin D level with multiple atherosclerosis-promoting risk factors like BMI, total cholesterol, TG, HDL, systolic blood pressure value or exposure for tobacco [12, 32]. Research concerning adults from

PubMed search strategy:

1. Carotid Stenosis [Mesh]

2. Carotid Intima-Media Thickness [Mesh]

3. Vitamin D [Mesh]

Search: (1 OR 2) AND 3

Cochrane search strategy:

#1 "Carotid Stenosis"
#2 "Carotid Intima-Media Thickness"
#3 "Vitamin D"

Search: (#1 or #2) and #3 (title, abstract, keywords)

Fig. 1. Search strategy of articles using MESH vocabulary in PubMed and Cochrane databases

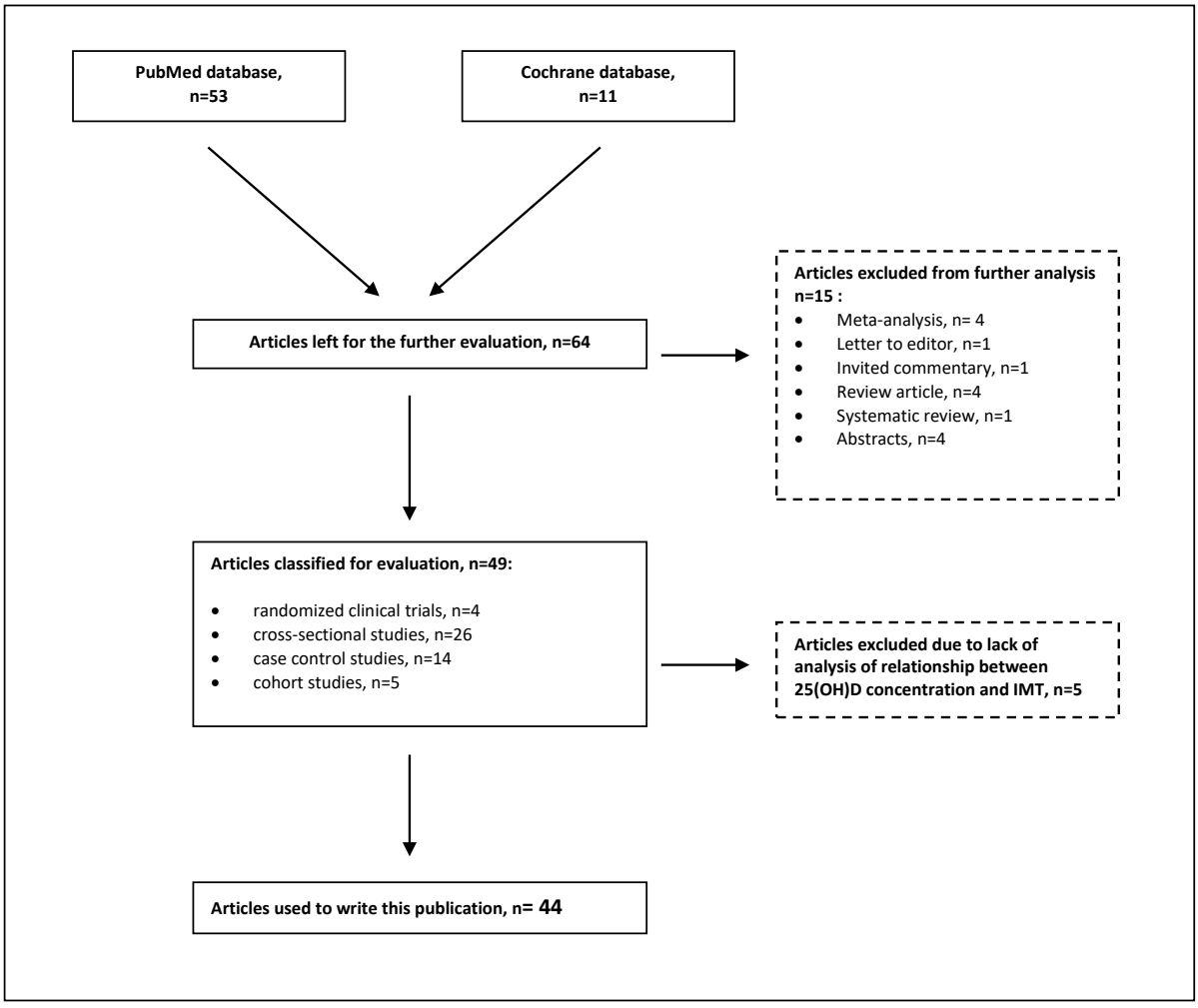

Fig. 2. Search strategy of articles about the concentration of vitamin D and the development of carotid stenosis

South Korea also indicates lack of relationship between the concentration of 25(OH)D and the value of IMT [13, 29]. Other studies including middle-aged and elderly subjects indicated no association between vitamin D levels and CIMT progression in 3.430 healthy participants who were burdened with cardiovascular disease risk. Statistical analyzes show that the concentration of vitamin D is not an efficient biomarker for the study of progression of subclinical atherosclerosis [16]. Likewise, analysis of collected data from a group of middle-aged and older men indicated that the concentration of 25(OH)D is inversely associated with atherosclerosis. It must be noted that the observed levels of vitamin D were low or indicated deficiency in that population [24]. Similar results were demonstrated by a research study involving adults who were recruited in childhood into Cardiovascular Risk in Young Finns Study. The analyzes indicated that in women, the 25 (OH)D concentration was inversely correlated with the IMT occurring at a later age of the subjects [28]. Changfeng Study conducted among middle-aged females assessed the relationship between serum 25(OH)D and carotid atherosclerosis in Chinese postmenopausal women. Individuals with 25(OH)D level in the fourth quartile (53.2–153.0 nmol/L) had significantly thinner CIMT and lower frequency of occurrence of carotid plaque compared to the rest of the participants. This study suggested an association between serum 25(OH)D and carotid atherosclerosis in postmenopausal women [37]. Another article involving Chinese postmenopausal women from Shanghai Obesity Study has shown that serum 25(OH)D level is negatively correlated with CIMT in vitamin D deficient population [25]. Gurses, et al. investigated the association between vitamin D deficiency and alternations of subclinical atherosclerosis markers. The correlation between vitamin D level and CIMT has not been found in vitamin D deficient population [22]. A study conducted on African women has shown that CIMT in lean women was positively associated with the PTH and $25(OH)D_3$ ratio and that an alternation in bone and calcium metabolism can influence arterial calcification in older African women; however, an association between CIMT and 25(OH)D alone was not found. It must be noted that the level of vitamin D in that population was optimal or high compared to other studies [20].

Vitamin D and Carotid IMT in metabolic disorders

Discordance in the examined matter has been found. Although some studies did not show any association between IMT progression and 25(OH)D level in prediabetic subjects and patients with type 1 or type 2 diabetes, a 2014 Shanghai study has proven a significant and independent inverse correlation between serum vitamin D level and carotid IMT in vitamin D deficient male subjects [11]. Two years later, cross-sectional observational research confirmed that serum 25(OH)D level inversely corresponded with left and right CIMT in type 2 diabetic patients with and without peripheral artery disease (PAD) [5, 35]. These results are in accordance with the multicenter, longitudinal Carotid Intima Media Thickness and IMT-Progression as Predictors of Vascular Events in a High Risk European Population (IMPROVE) cohort study in vitamin D deficient population, which shows that 25(OH)D decreasing allele of rs3829251 in the DHCR7 locus was correlated with faster progression of CIMT [55]. Recent research has indicated that vitamin D, K and Ca co-supplementation results in a decrease of maximum levels of left CIMT; however, mean levels of CIMT, compared with placebo group, have not been influenced. The study did not provide information about the concentration of the 25(OH)D metabolite [3].

Vitamin D and Carotid IMT in overweight and obese patients

25(OH)D deficiency may be a cardiovascular risk factor from childhood, because the association between low vitamin D status and increased CIMT has been proven in both obese children and adolescents [4]. A research study in 2015 involving 44 children has demonstrated that there is no significant association between CIMT and vitamin D level; however, antipsychotic drug intake was an unquestionable interfering factor. The children's population in the study group showed a deficiency of vitamin D, while children in the control group showed a decrease in vitamin D concentration [43].

Vitamin D and Carotid IMT in chronic kidney diseases

Chronic kidney disease (CKD) is evolving into one of the leading health problems, especially in industrialized countries. Increased atherosclerosis is a common complication in renal dysfunction. IMT is a useful detector of atherosclerosis and an inexpensive tool to monitor its arrest, progression or regression. Yadav and co-authors have shown that CKD patients exhibit higher CCA-CIMT and lower 25(OH)D levels compered to healthy control. There was also a strong inverse correlation between serum levels of the vitamin D and CIMT [62]. Contrary to these findings, Ng *et al.* have not found any association between serum 25(OH)D levels and CIMT in CKD vitamin D deficient patients, but what is notable is that their study participants had less severe CKD stages [42]. These findings advocate for a possible linkage between 25(OH)D concentration and atherosclerosis.

Vitamin D and Carotid IMT in autoimmune diseases

Among all enrolled studies, five referred to patients with inflammatory diseases. CIMT assessment and biochemical results including 25(OH)D concentration were performed and did not show any significant association between 25(OH)D concentration and CIMT in 27 patients with rheumatoid arthritis (RA) and reduced concentration of 25(OH)D [36]. The second original article concerned 25(OH)D_3 deficiency in 36 patients with Behçet's disease (BD) and 33 subject with RA. In the correlation analysis, no relationship was observed between 25(OH)D_3 and CIMT in BD. No difference was observed between the concentration of 25(OH)D_3in RA patients compared to healthy control subjects [8]. Also, analysis of the data collected in the Lupus Atherosclerosis Prevention Study (LAPS) did not find any relationship between 25(OH)D concentration and IMT progression [31]. However, in a study involving 25 women with primary Sjögren's Syndrome (pSS), who were compared with 22 age -matched osteoarthritic control women, there was a significant increase of IMT and a decrease of vitamin D concentration. Additionally, no correlation between low levels of vitamin D and IMT in women with pSS and a reduced level of vitamin D was observed [64]. A considerable part of the collected articles on autoimmune diseases indicated a lack of relationship between the concentration of 25(OH)D and IMT progression, but results of the collected data of patients with psoriasis show that the level of vitamin 25(OH)D is negatively associated with Maximum IMT (MIMT) values in comparison to the control group. Analyzes indicate that MIMT values were associated with lower 25(OH)D values in reference subjects and that the risk of MIMT increases regardless of patient's age, but the duration of disease is not affected by the assessment of vitamin D and MIMT relationship [44].

Vitamin D and Carotid IMT in cardiovascular disease

Several investigations have been conducted on the following matter. The effect of 25(OH)D deficiency on atherosclerosis was assessed. Curiously, a large number of respondents showed 25(OH)D deficiencies. Oz *et al.* have shown that 25(OH)D deficiency was correlated independently with CIMT [45]. 25(OH)D concentration in patients with occlusive or aneurysmatic arterial disease was investigated in reference to atherosclerosis markers and clinical cardiovascular risk profile. Low levels of 25(OH)D were associated with higher CIMT [57].

Vitamin D and Carotid IMT in human immunodeficiency virus (HIV) infection

Results of two original papers comparing vitamin D concentration with CIMT in HIV-infected patients with low vitamin D concentration show a lack of increased risk of developing cardiovascular disease (CVD). The first article was a cross-sectional observational study, which included

Table 1. Articles which met inclusion criteria

Autors	Study design	Study group				Control group				Results	References
		Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT	Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT		
Vitamin D and Carotid IMT in healthy people											
Knox S. et al.	cross-sectional study	666	participant of the pSoBid (a population no databased study which set out to investigate the psychological, behavioral and biological determinants of ill health), three age categories 35-44, 45-54, and 55-64 years	no data	no data	no data	no data	no data	no data	25(OH)D ↔ CIMT	[32]
Kang J.Y. et al.	cross-sectional study	1054	adults ≥ 40 years from rural area of South Korea, divided into 3 groups according to vitamin D intake	$25(OH)D_3$ [nmol/L] 66.25 ± 30.0 (M) 47.25 ± 15.75 (F)	CIMT [mm] 0.75 ± 0.14 (M) 0.69 ± 0.14 (F)	no data	no data	no data	no data	25(OH)D ↔ CIMT	[29]
van Dijk S.C. et al.	cross-sectional study	567	participants of B-PROOF study ≥ 65 y with elevated homocysteine level (12-50μmol/l)	25(OH)D [nmol/L] 54.6 ± 24.1	CIMT [mm] 0.717±0.1632	no data	no data	no data	no data	↑25(OH)D : ↑CIMT	[58]
Thiele I. et al.	cross-sectional study	1601	participants of the Cooperative Health Research in the Region of Augsburg (KORA) F4, participants aged 50-81 years	25(OH)D ($25(OH)D_2$ +$25(OH)D_3$) [nmol/L] 37.0 ± 16.5	no data	no data	no data	no data	no data	↓25(OH)D : ↑CIMT	[56]
Cheraghi N. et al.	cross-sectional study	74	children with multiple, modifiable atherosclerosis-promoting risk factors	25(OH)D [nmol/L] 65.25 ± 23.5	CIMT [mm] 0.54±0.07	no data	no data	no data	no data	25(OH)D ↔ CIMT	[12]
Hao Y. et al.	case control study	712	men aged 45-78 years with plaque	$25(OH)D_3$ [nmol/L] 25(OH)D 34.5 (27.05 – 44.2)	no data	289	men aged 45no data78 years without plaque	$25(OH)D_3$ [nmol/L] 36.85 (27.17– 47.7)	no data	↓25(OH)D : ↑CIMT	[24]
Choi Y.K. et al.	case control study	43	healthy participants with 25(OH)D deficiency	25(OH)D [nmol/L] 40.0 ± 8.0	CIMT [mm] 0.74±0.13	28	healthy participants with 25(OH)D non-deficiency	25(OH)D [nmol/L] 65.75 ± 16.0	CIMT [mm] 0.76±0.14	25(OH)D ↔ CIMT	[13]
Blondon M. et al.	cohort study	3 251	patients without cardiovascular diseases	no data	no data	no data	no data	no data	no data	25(OH)D ↔IMT	[7]
Deleskog A. et al.	cohort study	3 430	elderly and middle-aged participants with high cardiovascular risk and no prevalent disease	no data	no data	no data	no data	no data	no data	25(OH)D ↔ IMT	[16]

Autors	Study design	Study group				Control group				Results	References
		Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT	Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT		
Juonala M. et al.	cohort study	2 148	adult children from the Cardiovascular Risk in Young Finns Study, aged3–18 years (in 1980);Participants were re-examined at age 30–45years (in 2007)	25(OH)D [nmol/L] 59.2 ± 19.1	CIMT [mm] 0.627 ±0.096	no data	no data	no data	no data	↓25(OH)D : ↑IMT	[27]
Gafane L.F. et al.	cross-sectional study	434	African women (392 postmenopausal and 42 premenopausal)	25(OH)D_3 [nmol/L] Lean: 109.5 (59.75 – 161.5) overweight/ obese: 91.5 (52.0 – 144.25)	CIMT [mm] Lean: 0.73±0.16 overweight/ obese: 0.79±0.16	no data	no data	no data	no data	↑25(OH)D : ↑PTH/25(OH) D_3. 25(OH)D ↔ IMT	[20]
Ma H. et al.	cross-sectional study	671	normotensive and euglycemic postmenopausal women	25(OH)D [nmol/L] 43.6 ± 9.2	CIMT [mm] 0.703 ± 0.123	no data	no data	no data	no data	↑25(OH)D : ↓CIMT	[37]
Hao Y. et al.	cross-sectional study	926	postmenopausal women from China without carotid artery plaque or history of cardiovascular disease	25(OH)D3 [nmol/L] 27.57 (20.55 –36.75)	no data	no data	no data	no data	no data	↓25(OH)D_3 : ↑ CIMT	[25]
Stamate-lopoulos K. et al.	case control study	102	postmenopausal female patients with primary hyperparathyroidism	25(OH)D_3 [nmol/L] 43.5 ±30.5.2	CIMT [mm] 0.695 ± 0.1	102	female patients age and menopausal status	25(OH)D_3 [nmol/L] 59.5 ± 42.0	CIMT [mm] 0.740 ± 0.2	25(OH)D_3 ↔ CIMT	[54]
Gurses K.M. et al.	case control study	31	premonopausal women with deficient of vitamin D	25(OH)D [nmol/L] 26.5 ± 11.75	**CIMT [mm] 0.45 ± 0.02**	27	age and gender-matched control subjects	25(OH)D [nmol/L] 86.0 ± 25.75	**CIMT [mm] 0.44 ± 0.02**	25(OH)D ↔ CIMT	[22]
					Vitamin D and Carotid IMT in metabolic disorders						
Bhadra R. et al.	cross-sectional study	57	patients with type 2 diabetes	25OHD_3 [nmol/L] 80.25 ± 22.67	CIMT [mm] 0.68 ± 0.124	57	age, gender matched healthy volunteers	25(OH)D_3 [nmol/L] 99.5 ± 7.55	CIMT [mm] 0.57 ±0.053	↓25(OH)D : ↑CIMT	[5]
Li D.M. et al.	cross-sectional study	1028	patients with diabetes type 2 (none gastrointestinal disease, none routinely vitamin D took or dietary calcium supplements) with Peripheral arterial disease (PAD)	25(OH)D [nmol/L] 28.36 ± 16.50	IMT [mm] 0.733±0.06	no data	patients with diabetes type 2 (none gastrointestinal disease, none routinely vitamin D took or dietary calcium supplements) without Peripheral arterial disease (PAD)	25(OH)D [nmol/L] 75.22 ± 40.0	IMT [mm] 0.707 ± 0.06	↓25(OH)D : ↑IMT	[35]
Winckler K. et al.	cross-sectional study	415	patients with type 2 diabetes (214 patients with 25(OH)D <50 nmol/L and 201 patients with 25(OH)D ≥ 50 nmol/L	25(OH)D (25(OH)D_2 + 25(OH)D_3 [nmol/l] 48 (7 – 176)	CIMT [mm] 0.793±0.137	no data	no data	no data	no data	25(OH)D ↔ IMT	[60]

Autors	Study design	Study group				Control group				Results	References
		Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT	Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT		
Chen R.H. et al.	cross-sectional study	127	patients with type 2 diabetes with carotid plaques	25(OH)D ($25(OH)D_2$ + $25(OH)D_3$) [nmol/L] 49.0 (33.25 –64.32)	CIMT [mm] 1.05 ± 0.16	223	patients with type 2 diabetes without carotid plaques	25(OH)D ($25(OH)D_2$ + $25(OH)D_3$) [nmol/L] 57.97 (45.25 –75.15)	CIMT [mm] 0.83 ± 0.17	↓25(OH)D : ↑CIMT (M)	[11]
Sachs M.C. et al.	cross-sectional study		patients with type1 diabetes	25(OH)D ($25(OH)D_2$ + $25(OH)D_3$) [nmol/L] 63.3 ± 4.7	IMT [mm] 0.7291 ± 0.0187	no data	no data	no data	no data	25(OH)D ↔ CIMT	[53]
Zagami R.M. et al.	case control study	83, 62, 61	pre-diabetic patients with pre-diabetes according to only HbA1c (HbA1c 5.7-6.4% and NFG/NT); subjects with impaired fasting glucose and impaired glucose tolerance (IFG/IGT); new onset type 2 diabetes (HbA1c ≥ 6.5%)	25(OH)D [nmol/L] 54.25 (39.5 – 77.75) 53.25 (43.0 – 75.75) 48.5 (34.8 – 71.25)	IMT [mm] 0.72 (0.65-0.81); 0.76 (0.68-0.86); 0.78 (0.7-0.9)	80	without history of diabetes	25(OH)D [nmol/L] 57.75 (42.75 – 74.25)	IMT [mm] 0.66 (0.62-0.75)	25(OH)D ↔ IMT	[63]
Asemi Z. et al.	randomized clinical trial	33	overweight patients (BMI ≥ 25 kg/m^2 with type 2 diabetes and chronic renal disease, received daily placebo tablets for 12 weeks	no data	no data	33	overweight patients (BMI ≥ 25 kg/m^2 with type 2 diabetes and chronic renal disease, received 5 µg of vitamin D and 90 µg of vitamin K2 to form MK-7 and 500 mg Ca supplements as a tablet	no data	no data	25(OH)D ↔ IMT	[3]
Strawbridge R.J. et al.	cohort study	3 711	participants with at least three cardiovascular risk factors and without history or symptoms of cardiovascular disease	25(OH)D [nmol/L] 48.1 (34.9 – 62.1)	IMT [mm] 0.850 (0.741 – 0.997)	no data	no data	no data	no data	↑25(OH)D: ↓IMT	[55]
Vitamin D and Carotid IMT in overweight patients											
Atabek M.E. et al.	cross-sectional study	247	children and young people with obesity, BMI>95p, with or without metabolic syndrome (MS)	25(OH)D [nmol/L] MS(+): 52.52 ± 32.15 MS(-): 67.77 ± 39.15	CIMT [mm] MS(+): 0.105 ± 0.020 MS(-): 0.097 ± 0.015	no data	no data	no data	no data	↓25(OH)D : ↑CIMT	[4]
Nicol G.E. et al.	case control study	25	children (ages 6-19) treated with antipsychotic and other psychotropic drug therapies	25(OH)D [nmol/L] 46.0 (22.0 –83.5)	CIMT [mm] 0.51 (0.40–0.64)	19	untreated children (ages 6-19)	25(OH)D [nmol/L] 55.25 (28.75 –96.75)	CIMT [mm] 0.52 (0.43–0.60)	25(OH)D ↔ IMT	[43]
Vitamin D and Carotid IMT in chronic kidney diseases											

Autors	Study design	Study group				Control group				Results	References
		Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT	Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT		
Ng Y.M. et al.	cross-sectional study	100	patients with chronic kidney diseases in stage 3 or 4	25(OH)D [nmol/L] 39.83 ± 22.43	CCA-IMT [mm] 0.724 ± 0.227	no data	no data	no data	no data	25(OH)D ↔ CCA-IMT	[42]
Haci-hamdio-glu D.Ö. et al.	cross-sectional study	17	pedriatric patients undergoing peritonel dialysis	25(OH)D [nmol/L] 27.5 (12.5 – 87.5) $1,25(OH)D_2$ [pg/ml] 11 (2 – 106)	CIMT SDS [mm] 0.84 [(-0.67)-1.65]	no data	no data	no data	no data	25(OH)D; $1,25(OH)D$ ↔ CIMT SDS	[23]
Yadav A.K. et al.	cross-sectional study	101	non dialysis patient with 3-4 stage of chronic kidney disease	no data	no data	40	healthy volunteers with normal kidney function	no data	no data	↓$25(OH)D_3$: ↑CCA-IMT	[62]
Fontan M.P. et al.	case control study	237	patients treated with peritonel dialysis for more than 3 months, without any clinical background of cardiovascular disease	25(OH)D [nmol/L] 32.0 ± 13.75 $1,25(OH)D_2$ [pg/ml] 7.7 ± 4.8	CIMT[mm] 0.68 (0.13)	237	age and gender matched patients without chronic kidney disease	25(OH)D [nmol/L] 51.5 ± 21.0 $1,25(OH)D_2$ [pg/ml] 33.0 ± 14.4	CIMT [mm] 0.69 (0.14)	25(OH)D ↔ IMT	[47]
Arroyo D. et al.	case control study	2445	age 18-74 with chronic kidney disease in stage 3 or higher (glomerular filtration rate <60 ml/ min./1.73m^2)	no data	CIMT [mm] 0.725	559	age 18-74 with non-chronic kidney disease (glomerular filtration rate >60 ml/min./1.73m^2)	no data	no data	25(OH)D ↔ IMT	[2]
Vitamin D and Carotid IMT in autoimmune diseases											
Can M. et al.	case control studies	36, 33	patients with Behcet Disease and patients with Rheumatoid arthritis	no data	no data	51	healthy	no data	no data	$25(OH)D_3$ ↔ CIMT	[8]
Kiani A.N. et al.	randomized clinical trial	200	patients enrolled in the Lupus Atherosclerosis Prevention Study	no data	no data	no data	no data	no data	no data	25(OH)D ↔ CIMT	[31]
Orgaz-Molina J. et al.	case control study	44	psoriatic patients without arthritis, not undergoing systematic psoriasis therapy or any antidiabetic, antihypertensitive or lipid-lowering treatments	25(OH)D [nmol/L] 73.0 ± 22.9	MIMT [mm] 0.64116 ± 0.07677	44	age and gender-matched	25(OH)D [nmol/L] 95.0 ± 25.4	MIMT [mm] 0.62614 ± 0.11024	↓25(OH)D : ↑MIMT	[44]
Zardi E.M. et al.	case control study	25	female patients with Sjogren's Syndrome (pSS)	Vitamin D [nmol/L] 52.32	IMT [mm] 0.76	22	age and gender-matched female patients with mild osteoarthritic with no history of autoimmune diseases (OCp)	Vitamin D [nmol/L] 66.05	IMT [mm] 0.69	Vitamin D ↔ IMT	[64]
Lo Gullo A. et al.	case control study	27	Rheumatoidarthritis	25(OH)D [nmol/L] 57.5 ± 19.0	CIMT [mm] 1 ± 0.17	41	Matched health patients	25(OH)D [nmol/L] 79.25 ± 13.0	CIMT [mm] 0.76±0.13	25(OH)D ↔ CIMT	[36]

Autors	Study design	Study group				Control group				Results	References
		Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT	Sample size	Sample characteristics/ intervention	Vitamin D level	CIMT/IMT		
Vitamin D and Carotid IMT in cardiovascular disease											
Oz F. et al.	cross-sectional study	116	patients with undergone coronary angiography for suspected stable ischemic heart disease with normal and near-normal coronary arteries, with vitamin D insufficient	no data	IMT [mm] 0.89±0.24	106	patients with undergone coronary angiography for suspected stable ischemic heart disease with normal and near-normal coronary arteries, with vitamin D sufficient	no data	IMT [mm] 0.64±0.17mm	↓25(OH)D : ↑ CIMT	[45]
Kalkan G.Y. et al.	cross-sectional study	117	patients with underwent transesophageal echocardiography for various indications	25(OH)D [nmol/L] 62.0 ± 24.75	no data	no data	no data	no data	no data	↓25(OH)D : ↑ IMT	[28]
van de Luijtgaarden K.M. et al.	cross-sectional study	490	254 patients with symptomatic peripheral arterial disease and 236 patients with aortic aneurysm	25(OH)D [nmol/L] 57 ± 93	CIMT [mm] 0.97 ±0.31	no data	no data	no data	no data	↓25(OH)D : ↑CIMT	[57]
Chan Y.H. et al.	case control study	443	443 high-risk cardiovascular patients (coronary disease, ischemic stroke)	no data	no data	no data	no data	no data	no data	↑25(OH)D : ↓CIMT	[10]
Ameri P. et al.	case control study	165	adult patients with 1 or 2 primary hypertension	no data	no data	472	healthy participants of community-dwelling	no data	no data	↑25(OH)D : ↓CIMT	[1]
Vitamin D and Carotid IMT in in HIV (human immunodeficiency virus) infection											
Eckard A.R. et al.	cross-sectional study	30	HIV-infected youth and children	25(OH)D [nmol/L] 60.0 ± 87.5	CCA IMT [mm] 1.00 (0.70–1.25)	31	Health uninfected patients	25(OH)D [nmol/L] 35.0 ± 12.5	CCA IMT [mm] 1.00 (0.75–1.25)	25(OH)D ↔ IMT	[18]
Portilla J. et al.	cross-sectional study	89	non-diabetic adult men with HIV infection	25(OH)D [nmol/L] 52.2 ± 27.0	no data	no data	no data	no data	no data	25(OH)D ↔ IMT	[50]
Vitamin D and Carotid IMT in endocrine disorders											
Walker M.D. et al.	cross-sectional study	100	patients with primary hyperparathyroidism, 25(OH)D ≥ 50 nmol/L	25OHD [nmol/L] 91.0 ± 25.0	CIMT [mm] 0.945 ± 0.108	10	patients with primary hyperpara-thyroidism, 25(OH)D < 20 ng/ml	25OHD [nmol/L] 36.0 ± 10.25	CIMT [mm] 0.943 ± 0.115	25(OH)D ↔ CIMT	[59]
Carne-vale V. et al.	cross-sectional study	168	patients from Unit of Internal Medicine with no advanced liver or renal disease, primary hyperparathyroidism, neoplastic cachexia, severe obesity	25OHD [nmol/L] 33.0 ± 21.5	IMT [mm] 0.97 ± 0.26	no data	no data	no data	no data	25(OH)D ↔ IMT	[9]

Abbreviation: ↔ – no relationship; ↑ – increase; ↓ – decrease; IMT – Intima-Media Thickness; CIMT – Carotid Intima-Media Thickness; CCA-IMT – Carotid Artery Intima-Media Thickness; CIMT SDS – Carotid Intima-Media Thickness standard deviation
score; MIMT – maximal intima-media thickness; MS – metabolic syndrome; PTH – parathyroid hormone ; HIV – human immunodeficiency virus; F – Female; M – Male.

89 men living with HIV who were receiving treatment with two nucleoside reverse transcriptase inhibitors (NRTIs) with protease inhibitor (PIs) or HIV-infected men with a non-NRTI that never took PIs. The subjects were divided according to the method of treatment. The occurrence of vitamin D insufficiency was associated with greater common CIMT. There was no correlation between common CIMT and vitamin D concentrations. In multivariate linear regression model, there were no associations between common CIMT and vitamin D insufficiency [50]. The second article was also a cross-sectional study that involved 31 children and young adults infected with HIV with reduced concentration of 25(OH)D metabolite. No significant associations were found between concentrations of vitamin D and CIMT in study group [18].

Vitamin D and Carotid IMT in endocrine disorders

Relationship between deficiency of 25(OH)D and vitamin D concentration within the normal range was assessed in patients with Primary Hyperparathyroidism (PHPT) and subclinical Cardiovascular Disease. Cardiovascular Disease and vitamin D concentration within the normal range was assessed. Carotid structure between patients with normal and low 25(OH)D levels was compared and indicated that IMT levels were increased, regardless of 25(OH)D level [59]. Association between 25(OH)D concentration and parathyroid hormone (PTH) levels with CIMT was determined. There were no significant differences among patients with reduced vitamin D level, between IMT value and the level of 25(OH)D. Moreover, IMT did not show any significant association with 25(OH)D, PTH or PTH/25OHD ratio [9].

CONCLUSIONS

A review of publications available in PubMed and Cochrane databases prepared by our team indicates that it is difficult to assess the relationship between the concentration of 25(OH)D and the progression of intima-media thickness. Due to the high heterogeneity of incorporated publications, the meta-analysis, which is more powerful as a statistical tool, could not be used. The results of studies conducted so far are inconclusive. In 26 papers, no association was found between concentration of 25(OH)D and IMT progression. Thirteen publications from 44 indicated the significance of relationship between reduced concentration of 25(OH)D and IMT progression. Five articles have shown the opposite relationship. In 4 of these, an increase in the concentration of vitamin D metabolite and IMT reduction was observed, while one publication reported an increase in IMT with the parallel increase of concentration of the (25(OH)D). Another thing which should be taken into account is that there may be a non-linear association between vitamin D level and health effects, which affects the different results in the vitamin D deficient population compared to populations with an optimal level of vitamin D. Lack of information about vitamin D level also occurs in some manuscripts what further complicates to draw the conclusions. There were a few studies with populations whose vitamin D level was optimal or near-optimal, and most of the studies were carried out in a population with a low level or vitamin D deficiency. We observed numerous contradictions in the collected results. Most of the assembled manuscripts have acknowledged the lack of connection between healthy people and those suffering from various diseases. These contradicting results may be caused by comparing articles that very often are related to populations with different baseline characteristics, thus the limitation of this review is a small number of available studies as well as their different protocol (case control, cross sectional).

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