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Vitamin D deficiency and its associated factors among patients with type 2 diabetes mellitus: a systematic review and meta-analysis

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ABSTRACT

Objective The study intended to assess the pooled prevalence of vitamin D deficiency (VDD) and its associated factors among patients with type 2 diabetes mellitus (T2DM).

Design The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were employed to plan and conduct this systematic review and meta-analysis.

Data sources PubMed, Medline, Google Scholar, Web of Science, Science Direct and the Worldwide Science database were searched from their inception to 31 January 2023.

Methods Data were extracted using a standardised data extraction format prepared in Microsoft Excel. The inverse variance (I^2) test was used to evaluate the presence of heterogeneity across the included studies. To identify the possible source of heterogeneity, subgroup analysis was carried out. Funnel plot symmetry, Begg's and Egger's tests were used to evaluate the existence of publication bias. In addition, factors associated with VDD among patients with T2DM were examined. All statistical analyses were carried out with STATA V.14 software.

Results A total of 54 studies with 38 016 study participants were included in the study. The pooled prevalence of VDD among patients with T2DM was found to be 64.2% (95% CI 60.6% to 67.8%) with a substantial level of heterogeneity (I^2=98.2%; p<0.001). Results of the subgroup analysis indicated that the pooled prevalence of VDD among patients with T2DM was highest (70.9%) in African nations and lowest (57.1%) in Middle East countries. Being female (pooled OR (POR) 1.60, 95% CI 1.29 to 1.97), having poor glycaemic control (POR 2.50; 95% CI 1.74 to 3.59), hypertension (POR 1.21; 95% CI 1.08 to 1.36), obesity (body mass index ≥25) (POR 1.68; 95% CI 1.16 to 2.44), dyslipidaemia (POR 2.54, 95% CI 1.37 to 4.73), albuminuria (POR 2.22, 95% CI 1.71 to 2.95), nephropathy (POR 1.58; 95% CI 1.08 to 2.31) and retinopathy (POR 1.48: 95% CI 1.17 to 1.89) were predictors of VDD among patients with T2DM.

Conclusions More than half of patients with T2DM were suffering from VDD. Being female, having poor glycaemic control, hypertension, obesity, dyslipidaemia, albuminuria, nephropathy and retinopathy were the predictors of VDD among patients with T2DM.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our meta-analysis includes a greater number of potentially eligible worldwide articles, and screening and data extraction was performed in a duplicate manner representing a major strength of our study.
⇒ The absence of publication bias and a single study that affects the overall prevalence of vitamin D deficiency (VDD) among patients with type 2 diabetes mellitus increase the reliability of our findings.
⇒ Due to the cross-sectional nature of most of the included studies, the case-and-effect relationship could not be ascertained.
⇒ Variation in the definition of VDD across the included studies represents the limitation of our study.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by hyperglycaemia of sufficient magnitude to cause detrimental effects, which resulted from insulin resistance followed by dysregulation of insulin secretory responses and loss of beta-cell mass.[1 2]

T2DM is a multifactorial disease triggered by the interplay of many malfunctioning mechanisms that occur simultaneously. In addition to genetics which predisposes individuals to develop T2DM, many environmental factors such as physical inactivity, abnormal dietary practices and obesity contribute greatly to its development. Moreover, recent evidence suggests the existence of vitamin D deficiency (VDD) contribution to the pathogenesis of T2DM.[3–5]

Vitamin D is a vital fat-soluble vitamin that is derived from dietary sources, and up to 80% is produced by the synthesis in the skin under the influence of ultraviolet-B radiation from sunlight.[6] Vitamin D with its receptors presents in diverse cell types is presumed to play an important role in several cellular processes, including insulin secretion by

pancreatic beta-cells, tissue response to insulin, glycaemic control or in attenuating diabetic complications.[7]

Evidence suggested that there are several mechanisms whereby vitamin D may influence glycaemic control, insulin secretion and sensitivity. For instance, the vitamin D receptor (VDR) is expressed in insulin-producing beta-cells. Insulin-producing beta-cells also have the enzyme necessary for activating 25(OH) D to the active form 1, 25 dihydroxy vitamin D. Vitamin D may also stimulate the expression of the insulin receptor in peripheral tissues and thereby increase glucose transport.[7 8] Added to this, insulin synthesis and secretion is also a calcium-dependent process and can consequently be indirectly influenced by vitamin D, which is a known regulator of plasma ionized-calcium levels. Moreover, vitamin D had a significant influence on the subsiding of an inflammatory process in patients with T2DM.[9 10]

As recent investigations revealed, VDD could result from inadequate nutritional intake of vitamin D, increased catabolism of vitamin D, inefficient production in the skin or inadequate exposure to sunlight, and VDD could suppress pancreas secretion and insulin sensitivity which leads to persistent hyperglycaemia and associated complications.[11–13] A recent review also indicates the multiple impacts VDD and insufficiency on the outcome of patients with T2DM. The results showed a significant association of VDD or insufficiency and glycaemic control, diabetes-related complications, metabolic syndrome, risk of obesity and reduced quality of life.[14] Therefore, early recognition of VDD and maintaining its adequate level may be an alternative approach to improve glycaemic control and prevent or delay the progression of diabetes-related complications.

Even though different primary studies have assessed the prevalence of VDD and its associated factors, most of these studies were single-centred, with relatively small sample sizes, and their results showed substantial variation and inconsistency. Hence, this systematic review and meta-analysis was conducted with the aim of assessing the pooled prevalence of VDD and its associated factors among patients with T2DM by combining the studies from the existing literature.

The finding of the study would serve as baseline data for policy-makers and other concerned stakeholders for planning and implementing appropriate prevention and intervention strategies for patients with T2DM. The results of the study would also serve as baseline data for those researchers interested in the field to carry out further studies.

METHODS

Protocol, search strategy and study selection

A systematic review and meta-analysis was conducted to evaluate the pooled prevalence of VDD among patients with T2DM. The review was conducted in accordance with the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (online supplemental file 1).

Initially, Joanna Briggs Institute and PROSPERO databases were searched to check out whether a systematic review and meta-analysis was previously carried out or for the presence of ongoing projects related to the current topic. Then, a systematic search of the literature was performed by the authors to identify all applicable primary studies.

The literatures were explored using PubMed, Scopus, Google Scholar, African Journals Online, Web of Science, Cochrane Library and Wiley Online Library. While searching the literature the following key search terms and Medical Subject Headings [MeSH] “prevalence”, “magnitude”, “vitamin D”, “25(OH)-D”, “25-hydroxyvitamin D”, “deficiency”, “Hypovitaminosis D”, “associated factors”, “predictors”, “determinant”, “Type 2 diabetes mellitus”, “type 2 diabetes”, “diabetes Mellitus” and “diabetic patient” were used separately or in combination with the Boolean operator’s terms “AND” and “OR” (online supplemental file 2). Moreover, the reference lists of each retrieved article were also assessed to identify further applicable articles. The search incorporates all the studies published up to the 31 January 2023 and it was restricted to full texts, free articles, human studies and published in peer-reviewed journals in the English language.

Meanwhile, all the explored articles were exported into the EndNote V.X20 software, and afterward, the duplicate articles were removed. Then, a full screening of all the retrieved article titles, abstracts, full-text and the quality of the article based on the predefined eligibility criteria were assessed. Finally, the selected articles were compiled together.

Inclusion and exclusion criteria

All studies that reported the prevalence of VDD and/or its predictors among patients with T2DM were eligible for the study. However, studies that were not fully accessible after contacting the primary author twice via email; in case of our outcome of interest is not explained or if it is not possible to calculate from the available data; and studies with a poor quality score as per the stated criteria were excluded from this study.

Data extraction and quality assessment

The included studies were thoroughly reviewed, and the required information for the review were extracted and summarised using a clear data extraction spreadsheet format prepared in Microsoft Office Excel software by the two authors independently. If discrepancies between data extractors were observed, a third author was involved. For each of the included study information regarding the corresponding author, year of publication, the country where the study was conducted, study design, sample size, VDD diagnostic criteria, the prevalence of VDD and identified factors that are significantly associated with VDD was extracted. Two by two data for each assessed variable was also extracted.

The methodological quality of each illegible article was evaluated by two authors independently using the

Newcastle-Ottawa scale (NOS) quality assessment tool adopted for the quality evaluation of cross-sectional studies.[15] In studies with some limitations and biases, and when there was any disagreement between the reviewers related to the quality assessment, all authors participated and the final decision was made by consensus. Finally, the studies were taken into analysis if they scored ≥5 out of 10 points in three domains of ten modified NOS components.

Furthermore, the risk of bias in the selected studies was assessed by three authors independently using the risk of bias tool for prevalence studies developed by Hoy *et al*.[16] The assessment tool consists of 10 parameters and failure to satisfy for each parameter was scored as 0 (no). Then scores were summed across items to generate an overall quality score ranging from 0 to 10. Any disagreements at the time of data abstraction were resolved by discussion and consensus. When the available data were not adequate to assist in making a judgement for a certain item, we contacted the corresponding authors for additional information and if uncertainty persists we decided to grade that item as 0 (failure to satisfy a specific item) meaning a high risk of bias. Finally, each article scored 8 or more 'yes' answers out of a 10-point scale was considered to be a low risk of bias; 5–7 'yes' answers were considered a moderate risk of bias; 4 or fewer 'yes' answers were considered to be a high risk of bias.

Statistical methods and analysis

The heterogeneity across the included studies was evaluated by I^2 statistics. In this meta-analysis, the heterogeneity tests revealed the occurrence of significant heterogeneity among the included studies (I^2=98.2%; p<0.001). Thus, a random-effects model was employed to estimate the pooled prevalence of VDD among patients with T2DM. Then the pooled prevalence along with their corresponding 95% CI was generated and presented using a forest plot. In addition, the probable sources of heterogeneity were explored by subgroup and meta-regression analysis. Furthermore, to assess the relative influence of each study on the overall estimate, sensitivity analysis was conducted by omitting each study one by one. Besides these, the evidence of publication bias was evaluated by using funnel plot symmetry, Egger's regression test and Begg's test. Finally, the different predictors of VDD among patients with T2DM were presented using pooled ORs (PORs) with a corresponding 95% CI. All statistical analyses were conducted using the STATA V.14 software (StataCorp).

Patient and public involvement

None.

RESULTS

Selection of the studies

A total of 8194 records regarding the prevalence and/or associated factors of VDD among patients with T2DM were retrieved using electronic database searches. Of these, 519 studies were excluded due to duplication. After assessing the title and abstract, 7547 were also excluded as they were found to be non-applicable for this systematic review and meta-analysis. The remaining 128 full-text studies were then evaluated for eligibility based on the predefined eligible criteria, which resulted in the further exclusion of 74 articles. Finally, 54 studies that fulfilled the eligibility criteria were incorporated in this systematic review and meta-analysis (figure 1).

Baseline characteristics of included studies

In this systematic review and meta-analysis, a total of 54 original studies published between 2006 and 2022 that showed the prevalence and associated factors of VDD among 38 016 patients with T2DM were included. The sample size of the included studies ranged from 60 in Egypt[17] to 9841 in Denmark[18] and 39 (72.2%) of the studies were cross-sectional. The highest prevalence of VDD was stated in the study conducted in Ghana (92.4%),[19] while the lowest was stated in the study conducted in Iran (24.0%)[20] (online supplemental file 3).

Prevalence of VDD

The pooled prevalence of VDD among patients with T2DM was estimated to be 64.2% (95% CI 60.6% to 67.8%) with a significant level of heterogeneity as evidenced by I^2 statistic (I^2=98.2%; p<0.001). This finding indicates a great variability in the prevalence of VDD among patients with T2DM across the included studies (figure 2).

Subgroup and meta-regression analysis

To identify the possible source of heterogeneity across the included studies, subgroup analysis based on the region where the study was conducted, study design, years of publication, risk of bias of the study and sample size were conducted. Results of the subgroup analysis revealed that the pooled prevalence of VDD among patients with T2DM was 70.9% in African nations and 57.1% in Middle East countries; 64.1% among studies published in 2018 or later and 64.3% among the studies published before 2018; 67.0% among studies with moderate risk of bias and 59.8% among studies with low risk of bias; and 63.7% among cross-sectional studies and 66.9% among case–control studies. The subgroup analysis also showed that the pooled prevalence of VDD among the studies with a sample size greater than the median (>202) of the total sample size was slightly higher than the studies with a sample size below the median of the total sample size (64.7% vs 63.5) (table 1). Moreover, meta-regression analysis has been conducted by considering year of publication, and sample size. However, none of these variables was statistically significant for the presence of heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed to evaluate the effect of each study on the pooled estimated prevalence of VDD among patients with T2DM by using the leave-one-out

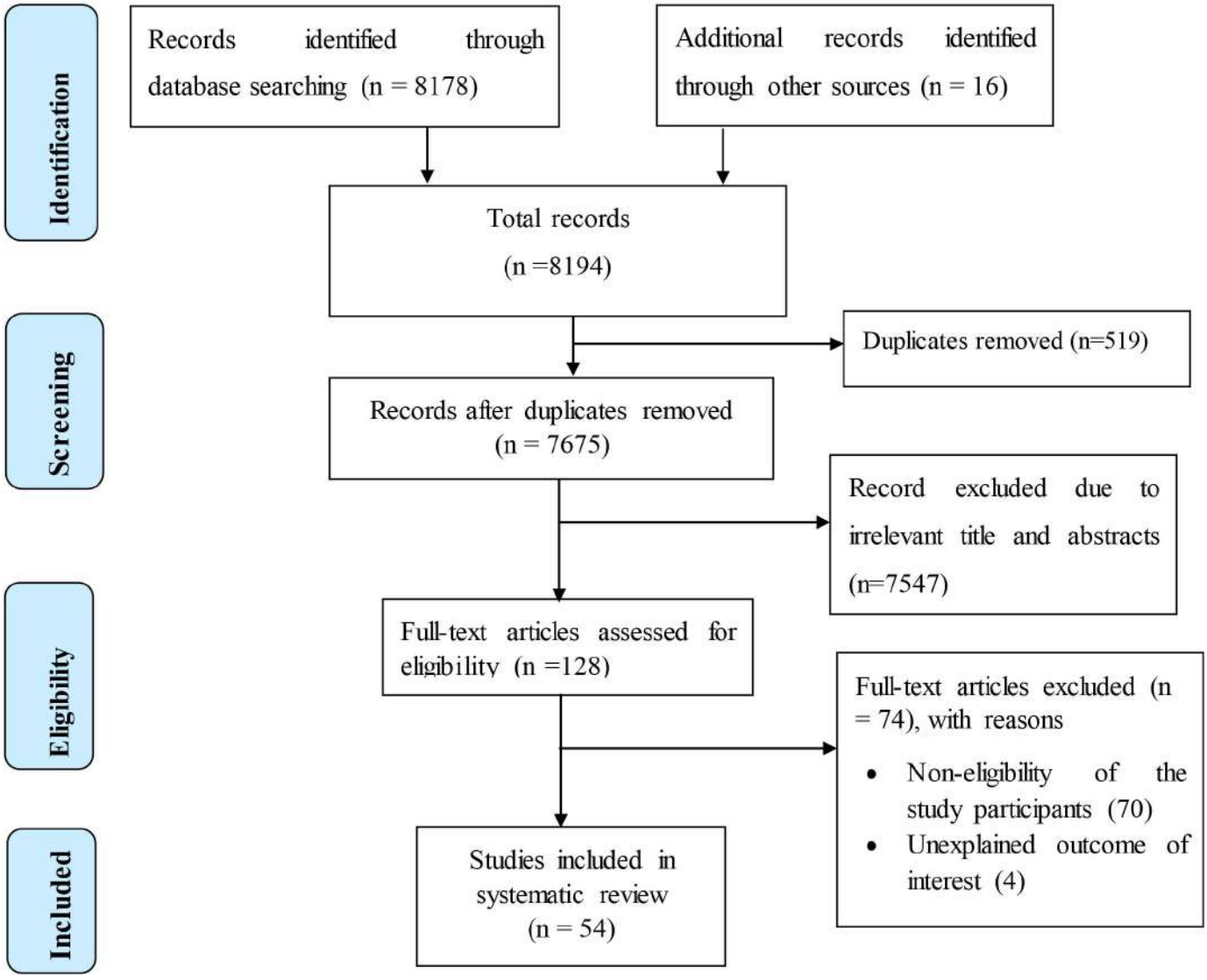

Figure 1 Flow chart showing the selection of studies for the systematic review and meta-analysis of the prevalence of vitamin D deficiency and its associated factors among patients with T2DM. T2DM, type 2 diabetes mellitus.

approach, excluding each study step-by-step from the analysis. The results showed that there was no single study that affects the overall prevalence of VDD among patients with T2DM.

Publication bias

The graphical inspection of the funnel plot was symmetrical in distribution indicating the absence of publication bias among the included studies (figure 3). Egger's (p=0.629) and Begg's test (p=0.123) computed to prove the existence of publication bias, also revealed no evidence of publication bias among the included studies.

Factors associated with VDD among patients with T2DM

Data regarding the associated factors of VDD among patients with T2DM were extracted from the available studies and the results were summarised in table (table 2).

Sociodemographic characteristics

Sociodemographic factors such as age, gender, smoking and drinking status of the study participants were included in this analysis. A total of two studies were included to define the association between participants' age (≥70) and VDD. Both of the included studies showed a non-significant association between participants' age (≥70) and VDD. In the final model, the pooled odds of VDD among participants aged ≥70 years is also statistically insignificant (POR 1.35; 95% CI 0.63 to 2.92).

A total of 20 studies were also included to find out the association between the sex of the participants and VDD, and 14 of the studies revealed a significant association. Of these studies that revealed a significant relation, 12 of them showed a significant association between being female and VDD while the remaining two studies showed the presence of a significant association between being male and VDD. There was a significant heterogeneity (I^2=87.7%, p<0.001) among the studies, and no influential

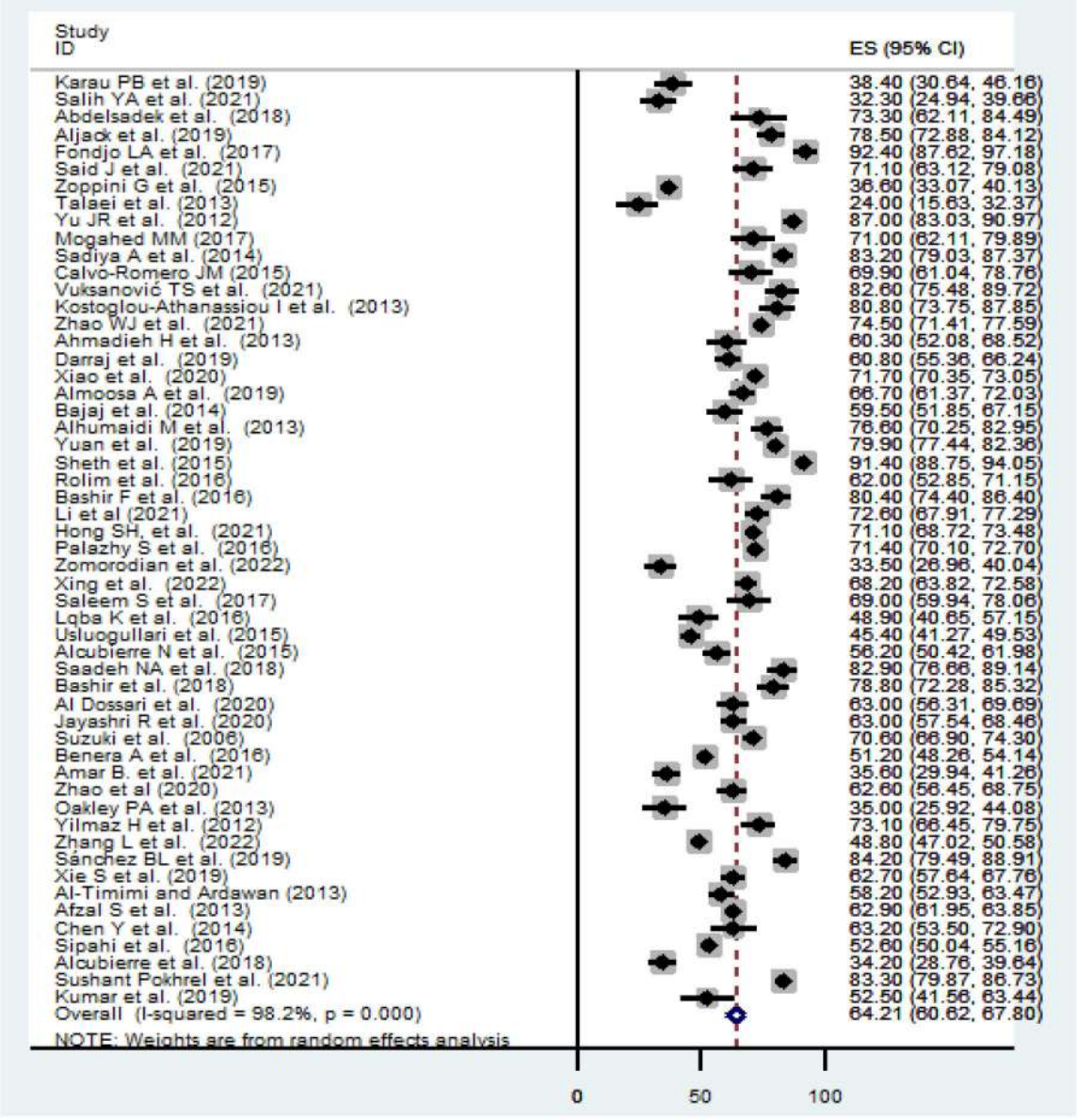

Figure 2 Forest plot of the pooled prevalence of vitamin D deficiency and its predictors among patients with type 2 diabetes mellitus, 2023. ES, Estimated.

study caused variations by the sensitivity analysis. There was no publication bias (Begg's test, p=0.697; Egger's test, p=0.654). The final pooled effect indicated that there was a significant association between being female sex and VDD (POR 1.60; 95% CI 1.29 to 1.97). Because of the appearance of statistically significant heterogeneity, the random-effect model was used during the analysis.

The pooled results from a total of 10 studies that assessed smoking status showed that there was no statistically significant association between smoking status and VDD among patients with T2DM (POR 0.90; 95% CI 0.74 to 1.11: I^2=72.3%, p<0.001). There was no influential study that caused variation and no publication bias was detected (Egger's test, p=0.806; Begg's Test, p=0.325). Likewise, a total of four studies were considered to determine the association between alcoholic drinking status and VDD, and three studies showed a significant association while the remaining one study showed a non-significant association. There was no influential study that caused deviations by the sensitivity analysis and no publication bias was detected (Egger's test, p=0.665; Begg's Test, p=0.99). The overall POR showed the absence of a statistically significant association between having a habit of alcoholic drinking and VDD (POR 0.89; 95% CI 0.60 to 1.33: I^2=84.7%, p<0.001).

Medical factors

Hypertension (HTN), level of glycaemic control (glycated haemoglobin, HbA1c), body mass index (BMI), dyslipidaemia and albuminuria were the medical factors considered in the analysis. To determine the association between glycaemic control and VDD, total of 10 studies were included. Eight out of 10 studies showed a significant association between the level of glycaemic control

Table 1 Subgroup analysis of the prevalence of vitamin D deficiency among patients with T2DM

Subgroup	Category	No of studies	Sample size	Prevalence (95% CI)	Heterogeneity	P value	I^2 (%)	Tau-squared
Region	African nations	5	658	70.9 (52.8 to 88.9)	137.70	0.000	97.1	407.48
	Middle East countries	17	6035	57.1 (49.8 to 64.5)	568.82	0.000	97.2	229.98
	European countries	8	11 693	63.3 (51.7 to 74.8)	453.92	0.000	98.5	269.94
	East Asian countries	12	12 806	69.5 (62.8 to 76.2)	689.95	0.000	98.4	133.85
	South Asia	10	6610	70.4 (62.9 to 77.8)	293.66	0.000	96.9	132.93
	South America	1	108	22.2 (14.4 to 30.0)	0.000	–	–	0.000
	North America	1	106	35.0 (25.9 to 44.1)	0.00	–	–	0.0000
Years of publication	≥2018	27	15 590	64.1 (58.7 to 69.5)	1321.1	0.000	98.0	194.4
	<2018	27	22 426	64.3 (59.1 to 69.6)	1557.8	0.000	98.3	183.2
Sample size	≥202	30	34 831	64.7 (60.2 to 69.2)	2255.6	0.000	98.7	151.9
	<202	24	3185	63.5 (55.6 to 71.4)	628.72	0.000	96.3	371.8
Risk of bias	Low risk	21	14 390	59.8 (53.6 to 66.1)	1188.0	0.000	98.3	204.7
	Moderate	33	23 626	67.0 (62.4 to 71.6)	1635.0	0.000	98.0	170.7
Study design	Cross-sectional	39	24 530	63.7 (59.3 to 68.1)	2123.6	0.000	98.2	188.2
	Case–control	13	2533	66.9 (55.2 to 78.6)	587.0	0.000	98.0	449.6
	Cohort	2	10 953	57.1 (45.0 to 68.6)	55.11	0.000	98.2	67.2

T2DM, type 2 diabetes mellitus.

and VDD, while the remaining two studies did not; and there was no prominent study that caused variation among the included studies. The overall pooled effect results indicated that patients with T2DM with poor glycaemic control (HbA1c≥7 were more likely to have VDD than their counterparts (POR 2.50; 95% CI 1.74 to 3.59: I^2=72.1%, p=0.000).

Additionally, to determine the association between HTN and VDD, a total of seven studies were included and six of them showed a non-significant association. There was no significant heterogeneity (I^2=0.0%, p=0.561), and publication bias (Egger's test: p=0.931; Begg's: p=0.293) among the studies. The final nonrandom pooled effect results showed the existence of a significant association between the presence of HTN and VDD among T2DM (POR 1.21; 95% CI 1.08 to 1.36).

To determine the association between BMI and VDD among patients with T2DM, seven studies were included and it was found that pooled odds of VDD among patients with T2DM with obesity (BMI≥25) is nearly two folds (POR 1.68; 95% CI 1.16 to 2.44) than their counterparts with a significant heterogeneity as evidenced by I^2 statistics (I^2=66.0%; p=0.007). On the other hand, the pooled result from seven studies showed patients with T2DM with dyslipidaemia had a higher pooled odd of VDD (POR 2.54; 95% CI 1.37 to 4.73; I^2=89.7%: p<0.001) than those without dyslipidaemia. Moreover, the pooled results from three studies showed that the pooled odds of VDD among patients with T2DM with albuminuria were two times more than those without albuminuria (POR 2.25; 95% CI 1.71 to 2.95). There was no significant heterogeneity (I^2=0.0%: p=0.792) among the included studies and the nonrandom effect model has been used for estimating POR.

Diabetic-related microvascular complications

Diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR) were the factors that have been reported by the studies included in the review. A total of eight studies were included to define the relation between DPN and VDD among patients with T2DM and only two of the studies showed the presence of a significant association. In the final random-effect model, the association between VDD and the presence of DPN was found to be statistically insignificant (POR 1.27; 95% CI 0.93 to 1.73) with substantial heterogeneity (I^2=75.5%: p<0.001).

Additionally, a total of seven articles were incorporated to evaluate the association between DN and VDD. Five of the included studies showed positive and significant association, one study showed a negative and significant association while the remaining studies revealed insignificant association between DN and VDD. Despite the presence of heterogeneity (I^2=83.1%, p<0.001) among subgroups, there was no dominant study that caused variation by sensitivity analysis and no publication bias (Egger's test: p=0.320; Beggar test: p=0.652). The final pooled effect size indicated that the odds of having VDD

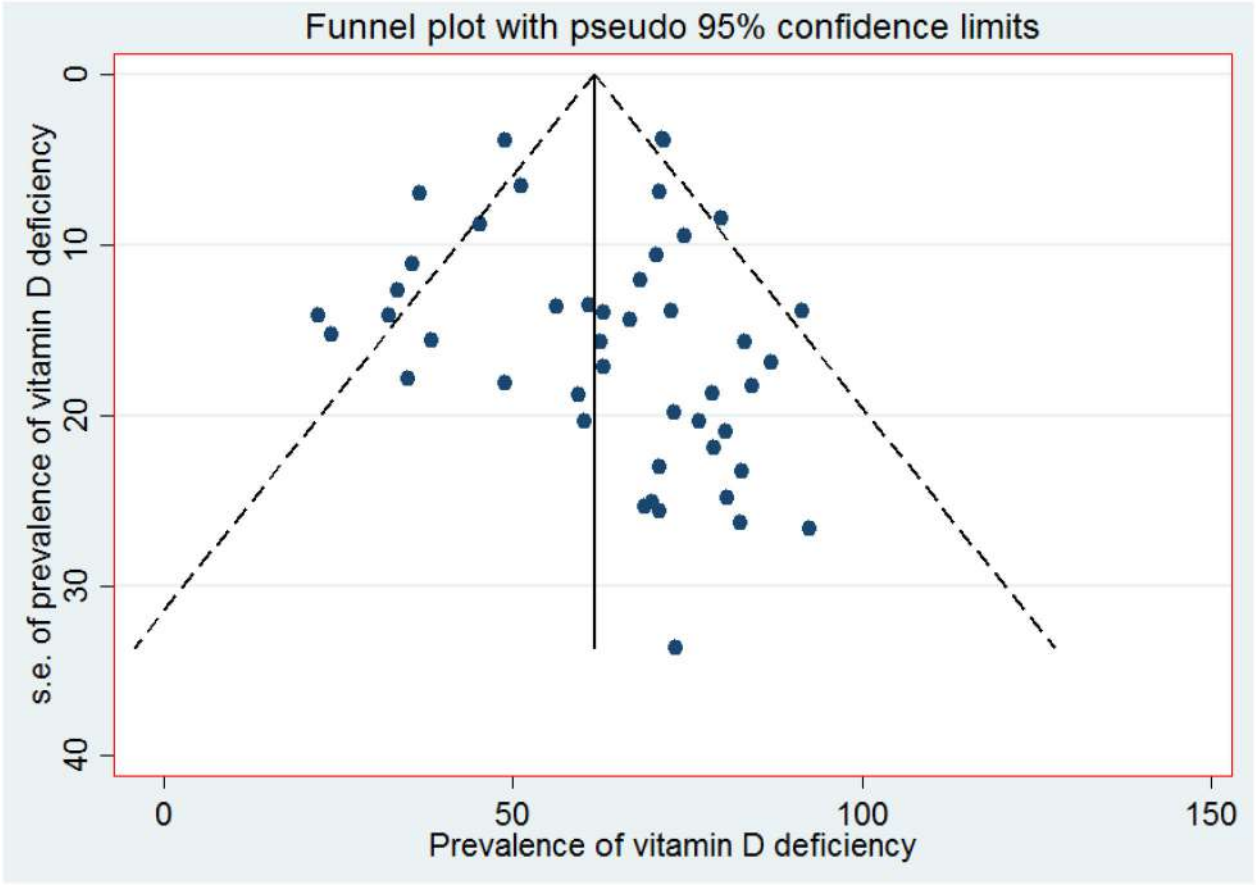

Figure 3 Test of publication bias of 54 included studies using a funnel plot.

among patients with T2DM with DN were approximately two times more than their counterparts (POR 1.58; 95% CI 1.08 to 2.31).

Likewise, a total of 10 studies were incorporated to determine the associations between DR and VDD. Five of them showed positive and significant association between

Table 2 Summary of the predictors of vitamin D deficiency among patients with T2DM

No	Identified factors	No of included studies	POR (95% CI)	P value	Heterogeneity		Publication bias (Egger's test)	Range of results by omitted one study at a time	
					P value	I^2	P value	Mini	Max
1	Age ≥70 years	2	1.35 (0.63 to 2.92)	0.440	0.00%	0.744	--	0.81	1.60
2	Sex (female)	20	1.60 (1.29 to 1.97)	0.000	87.7%	<0.001	0.654	1.061	1.25
3	Smoking status	10	0.90 (0.74 to 1.11)	0.325	72.3%,	<0.001	0.806	0.89	1.07
4	Drinking status	4	0.89 (0.60 to 1.33)	0.584	84.7%	<0.001	0.665	0.79	1.39
5	Hypertension	7	1.21 (1.08 to 1.36)	0.001	0.0%	0.561	0.931	0.96	1.16
6	Glycaemic control (HbA1c >7)	10	2.50 (1.74 to 3.59)	0.000	72.1%	<0.001	0.339	1.17	1.86
7	BMI≥25	7	1.68 (1.16 to 2.44)	0.006	66.0%	0.007	0.148	0.99	1.53
8	Dyslipidaemia	7	1.69 (1.06 to 2.70)	0.027	79.8%	<0.001	0.225	0.94	1.82
9	Albuminuria	3	2.25 (1.71 to 2.95)	<0.001	0.0%	0.792	0.554	0.83	2.13
10	Diabetic-neuropathy	8	1.27 (0.93 to 1.73)	0.135	75.5%	<0.001	0.933	0.96	1.27
11	Diabetic nephropathy	7	1.58 (1.08 to, 2.31)	0.018	83.1%	<0.001	0.320	1.00	1.38
12	Diabetic retinopathy	9	1.48 (1.17 to 1.89)	0.001	69.7%,	<0.001	0.178	1.04	1.36

BMI, body mass index; HbA1c, glycated haemoglobin; POR, pooled OR; T2DM, type 2 diabetes mellitus.

the presence of DR and VDD, four of them showed positive and insignificant associations, and one study showed a negative and insignificant association. The final pooled effect result indicates the presence of significant association between DR and VDD (POR 1.48; 95% CI 1.17 to 1.89: I^2=69.7%, p<0.001). Influential study that caused variations and publication bias were not observed (Egger's test: p0.178; Beggar test: p=0.325).

DISCUSSION

This systematic review and meta-analysis was carried out to estimate the worldwide burden of VDD and its associated factors among patients with T2DM. The reviewed results revealed that the pooled prevalence of VDD among patients with T2DM was found to be 64.2% (95% CI 60.6% to 67.8%). This finding is comparable with results from the studies conducted in Bahrain (66.7%),[21] Brazil (62.0%),[22] Denmark (62.9%),[18] Lebanon (60.3%)[23] and Saudi Arabia (60.8–63.0).[24 25] However, the prevalence of VDD in this review is lower than the studies conducted in Egypt (73.3%),[17] Sudan (78.5%),[26] Ghana (92.4%),[19] Korea (71.1%–87.0%),[27 28] China (71.7%–79.9%),[29 30] Pakistan (78.8%–80.4%),[31 32] India (71.4%–91.4%)[33 34] and Japan (70.6%).[35] In contrast, the prevalence of VDD in this review is higher than the studies conducted in Iran (24.0%–33.5%),[20 36] Iraq (32.3%–53.7%),[37 38] Italy (36.6%),[39] Turkey (45.4%),[40] Spain (56.2%)[41] and Qatar (51.2%).[42]

These variations in the prevalence of VDD among patients with T2DM may be due the variations in sociodemographic characteristics, geographical location of the study areas, the quality of healthcare services and health-seeking behaviour of the participants, the definition of VDD, methodology and the eligibility criteria of the included studies. Since the level of vitamin D is determined by the availability of sunlight exposure, this discrepancy in the prevalence of VDD may be due to the variation of seasons when the studies were conducted.

Although only one study from South America, and North America was found with a prevalence of 22.2% (95% CI 14.4% to 30.0%) and 35.0% (95% CI 25.9% to 44.1%), respectively, subgroup analysis of the included studies indicated that the prevalence of VDD among T2DM varies greatly with the highest prevalence was observed from African regions 70.9% (95% CI 52.8% to 88.9%) while the lowest prevalence was from European countries 57.4% (95% CI 48.3% to 64.4%). The explanation for this variation in the prevalence of VDD across the region may be due to the facts that variation in sunlight exposure and the colour of the skin that influence the dermal generation of vitamin D. Despite the plenty of sunshine all over the year in the majority of African regions, people may avoid sun exposure because of high ambient temperatures and hence they are more vulnerable for VDD. Additionally, due to adaptation to prevent skin damage from the sunny African climate, those who live in Africa have large amounts of melanin in their skin and this reduces the effectiveness of vitamin D synthesis from the sun.[43–45] Less implementation of VDD intervention policies and less availability of vitamin D-fortified food in Africa may also be another possible explanation for the high prevalence of VDD in the African region.

Time-based subgroup analysis also revealed that the prevalence of VDD from 2018 to the recent 65.0% (95% CI 59.4% to 70.6%) was higher than the prevalence before the year 2018 (63.5% (95% CI 56.1% to 70.8%)). This indicates the increasing trend of VDD among patients with T2DM; probably due to the adoption of an unhealthier lifestyle accompanied by minimal outdoor activities and lower sun exposure because of globalisation.

This review also tried to identify factors associated with VDD among patients with T2DM using the results of the primary studies and it was found that being female, having poor glycaemic control, HTN, poor glycaemic control, obesity (BMI≥25), dyslipidaemia, albuminuria, DN and DR were significantly associated with the existence of VDD among patients with T2DM.

In this review, being female was significantly associated with VDD among patients with T2DM in which the odds of developing VDD among female patients was approximately two times more than that of their counterparts. This result is in accordance with the previous studies conducted in Sudan,[26] Saudi Arabia,[46] Brazil,[22] Iraq[37] and Korea.[27] The rationale may be due to physiological variation related to sex. Since vitamin D is a fat-soluble, greater subcutaneous fat in females than males which is closely related to oestrogen, can store large amounts of vitamin D molecules produced from the skin, which leads to a decrease of circulating vitamin D molecules in females than in males.[47 48] Cultural and religious reasons that may enforce females to have lower outdoor activities, cover all their body with clothes, and wear a hijab when they go outdoors can reduce the surface area exposed to direct sunlight even where they live in a sunny climate would also be another possible explanation for the existence of significant association between being female and VDD.

Concurrent with previous findings,[22 26 29 37] the results of this review revealed that patients with T2DM with obesity had an increased risk of VDD than their counterparts. It is noteworthy that VDD is communal in persons with high BMI. The explanation might be due to the great capacity of adipose tissue to sequester vitamin D and thus making it biologically unavailable.[49] Another possible explanation may be related to the serum level of leptin. In vivo experimental study, leptin has decreasing effects on 1α(OH)ase and 24(OH)ase activities, and corrects elevated calcium, phosphate, and 1,25(OH)2D3 levels, implicating the role of leptin in down-regulating 1,25(OH)2D3 synthesis. Interestingly, the serum level of leptin is positively correlated with obesity. Hence, in the condition of obesity, there may be excessive down-regulation of 1, 25(OH) 2D3 levels that may lead to VDD.[50]

In addition, this study demonstrated that patients with T2DM with poor glycaemic control (HbA1c≥7) had a

high risk of VDD than those with good glycaemic control. This finding was in accordance with the results of the study conducted in Korea,[27] Saudi Arabia,[24] Pakistan[51] and China.[52] It is not surprising to see a significant association between VDD and markers of glycaemic control (HbA1c) in this review, as various previous experimental studies[33 53 54] also revealed such a situation. This may be due to the fact that vitamin D is positively correlated with beta-cell insulin secretion and insulin sensitivity in the target organ. This is because vitamin D directly stimulates the insulin receptor, increasing the insulin response to glucose by binding its active circulating form to its receptor in beta-cells.[7–9] This is supported by the finding of vitamin VDR in beta-cells and the finding of impaired insulin secretory capacity in mice lacking a functional VDR indicating an important role of vitamin D in regulating beta-cell function.[55] In peripheral insulin-target organs, vitamin D might also directly enhance insulin action through stimulation of insulin receptors gene expression and regulation of insulin-mediated intracellular processes.[7 9] Additionally, vitamin D has indirect effects on insulin secretion and sensitivity via the regulation of calcium levels. Calcium is required for insulin secretion from pancreatic beta-cells because of its action on membrane depolarisation and triggering of exocytosis in the process of insulin secretion. Calcium is also an essential factor for the transport of glucose to insulin-target tissue by stimulating glucose transporter.[9 56 57]

This review result revealed that dyslipidaemia is other predictors of VDD among patients with T2DM in which respondents with dyslipidaemia were three times more likely to have VDD than those with a normal lipid level. This could be due to an increase in the secretion of parathyroid hormone (PTH) secondary to a low level of vitamin D. Increased PTH level enhances lipogenesis, decreases lipolytic activity and can promote calcium influx into the adipocytes resulting in a high triglyceride (TG) level.[58 59] Furthermore, inadequate vitamin D levels can decrease the rate of calcium absorption from the small intestines whereby insoluble calcium–fatty acid complexes are formed and consequently inhibit the intestinal absorption of fatty acids. Reduced absorption of saturated fatty acids and other fats results in lower levels of cholesterol in the serum.[60 61] One further route is that VDD has a corresponding effect on beta-cell function, which leads to insulin resistance, disturbance of lipoprotein metabolism, and ultimately, increased TG and decreased high-density lipoprotein levels. In addition, vitamin D may have a direct influence on lipid metabolism and is known to play a part in the synthesis of bile acids in the liver.[62 63] Therefore, it is most likely that several processes act simultaneously which results in a significant linkage between VDD and dyslipidaemia.

In agreement with the finding of Chida *et al*,[64] Huang *et al*,[65] Xie *et al*,[66] Felício *et al*[67] studies, our results showed that patients with T2DM with albuminuria had an increased risk of VDD than those without albuminuria. This may be due to the anti-inflammatory and anti-fibrotic effects of vitamin D.[68] Hence, VDD will be linked with increased levels of inflammatory markers and substances that have fibrotic effects. These may lead to further glomerular damage, common in patients with T2DM, and enhanced macromolecule permeability in the glomerulus.[69] Moreover, vitamin D has suppressive effects on the renin-angiotensin-aldosterone system (RAAS), the main renal injury player, so that it has a protective activity on the kidney.[36] During VDD, the suppressive effects of vitamin D on the RAAS will be diminished and resulted in glomerular damage and proteinuria, particularly albuminuria.

It was also likely that the variation in the prevalence of VDD among patients with T2DM might result from the presence of diabetic-related microvascular complications. Despite whether VDD is the cause or the effect of microvascular complications is unknown, the presence of microvascular complications is significantly associated with the existence of VDD in which patients with either DN or DR were approximately three times more likely to have VDD than their counterparts. Since emerging evidence showed that DR and DN are initiated and propagated by inflammation and angiogenesis, the putative mechanism that might underlie this association is the anti-angiogenesis and anti-inflammatory effects of vitamin D.[39] Experimental studies showed the extensive expression of VDR in the retina and kidney. Due to these facts, vitamin D might avert the initiation and progression of DR and DN as a result of its anti-inflammatory and antiangiogenic properties.[40 70] Hence, it is not surprising to see a significant association between VDD and the presence of microvascular complications (principally DR and DN) among patients with T2DM.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis on the prevalence of VDD and its associated factors among patients with T2DM. The review used a broad literature search of worldwide data; and screening, study selection, quality assessment and data extraction were carefully performed in a duplicate manner; which enabled the study to provide a reliable overview of the prevalence of VDD and its associated factors among patients with T2DM. These are some of the strengths of our study. Our assessments of sensitivity analysis and publication bias were also indicating additional strengths of our study. The results showed the absence of publication bias and a single study that affects the overall prevalence of VDD among patients with T2DM which also increases the reliability of our findings. This systematic review and meta-analysis has some limitations that need to be considered. There is some variation in VDD cut-off points in the included studies that may have effects on the pooled prevalence of VDD. Some of the studies included in the review were with a small sample size that could also influence the final estimate of VDD. Though the quality of the included studies was rigorously assessed, most of the studies included in the reviews were cross-sectional. As a result, a cause-and-effect relationship cannot be

ascertained. Moreover, there was substantial heterogeneity among the included studies and the cause/s for the heterogeneity thus remains undetected.

Conclusion

More than half of patients with T2DM were suffering from VDD. Being female, having poor glycaemic control, HTN, obesity, dyslipidaemia, albuminuria, nephropathy and retinopathy were the predictors of VDD among patients with T2DM. Hence, patients with T2DM particularly female patients, obese patients, patients with microvascular complications and patients with a comorbid condition such as HTN and dyslipidaemia should be monitored for VDD and its consequence.

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