British Journal of Nutrition (2022), 127, 972–981 doi:10.1017/S0007114521001707

Is diabetic neuropathy associated with vitamin D status? A meta-analysis

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(Submitted 19 October 2020 – Final revision received 9 May 2021 – Accepted 15 May 2021 – First published online 24 May 2021)

Abstract

Several studies have been conducted to investigate the relation between 25-hydroxyvitamin D [25(OH)D] level and diabetic neuropathy (DN). However, there is still no clear conclusion due to differences in study design and cut-off values used in the published work, in addition to the absence of a comprehensive meta-analysis (MA) on the topic. The present systematic review and MA therefore aims at clarifying the association between vitamin D level and peripheral DN in patients with type 2 diabetes mellitus. Primary research studies that explored the association between 25(OH)D level and diabetic peripheral neuropathy in type 2 diabetes were located from Medline, EMBASE, Web of Science, Cochrane Library, CINHAL and Google Scholar. Twenty-six studies met the inclusion criteria with 6277 participants where 2218 were diabetic with DN, 2959 were diabetic without DN and 406 were healthy. Diabetic patients with DN showed significantly lower serum 25(OH)D compared with patients without DN (standardised mean difference (SMD) of −0·92 (95 % CI −1·18, −0·65, $I^2 = 93{\cdot}3$ %, $P < 0{\cdot}0001$). The pooled OR value of vitamin D deficiency was higher in patients with DN, 1·84 (95 % CI 1·46, 2·33, $P < 0{\cdot}0001$) and 2·87 (95 % CI 1·10, 7·52, $P = 0{\cdot}03$) when using fixed-effects and random-effects models, respectively. Vitamin D deficiency has been found to be highly prevalent among diabetic patients with neuropathy. Since 25(OH)D has been implicated in glucose haemostasis and showed benefit in reducing neuropathy symptoms, its supplementation is warranted for this population of patients.

Key words: **Vitamin D: Diabetic neuropathy: Diabetes: Insulin resistance: Nutrition**

Diabetes and its complications represent major and increasing challenges to healthcare systems worldwide. According to the International Diabetes Federation in 2017, 425 million adults have diabetes in the World from whom one in two adults remains undiagnosed. In 2045, this number will rise to 629 million people.

One of the most common consequences of diabetes is the damage of the peripheral nervous system.[1,2] It is estimated that 50 % of diabetic patients end up having diabetic neuropathy (DN).[1,3] DN is a microvascular complication leading to nerve damage leading to high morbidity and mortality.[2] While the exact mechanism of DN is still unclear; male gender, increasing age, BMI, height and disease duration were identified as potential risk factors for DN.[4,5] Further, several studies have suggested that vitamin D deficiency could be an independent risk factor for DN.[2,5–8] Vitamin D is a steroid that functions as a hormone in the human body. It has also a role in glucose homoeostasis and sensitivity to insulin.[9] In addition, recent work has shown that patients diagnosed with vitamin D deficiency (serum level of 25-hydroxyvitamin D below 20 ng/ml) had a higher prevalence of DN than those who were diagnosed with insufficiency (20–30 ng/ml) or sufficiency (30–60 ng/ml).[8,10,11] Moreover, many studies suggest that the use of vitamin D supplementation could improve the symptoms of DN.[2,12–17]

Despite several studies, there appears to be no consensus among researchers with respect to the relation between 25-hydroxyvitamin D and DN. This may be due to differences in sample size, study design, participant ethnicity and cut-off values used in the published work. Moreover, to our knowledge, there are very few published meta-analyses about this relationship which only included between six and thirteen studies each that were either all cross-sectional or all case–control.[18–20] The present systematic review and meta-analysis (MA) therefore

Abbreviations: DN, diabetic neuropathy; MA, meta-analysis.

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aims at clarifying the association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus.

Methods

Search strategy

A specific search strategy has been elaborated to locate the maximum number of relevant studies using the following electronic databases: Medline, EMBASE, Web of Science, Cochrane Library, CINHAL, EBSCO and Google Scholar, from inception to 01 March 2020. The following Boolean terms were used [diabetic AND neuropathy AND (''vitamin D'' OR 25(OH)D OR ''25(OH) vitamin D'' OR ''25-hydroxy vitamin D'' OR ''25-hydroxyvitamin D'')]. No language or date limitations were imposed.

Criteria for study selection

All study types were accepted for inclusion but two: case reports and reviews. Only patients having type II diabetes were included. Studies reporting comparisons between healthy, diabetic patients without DN or diabetic patients with DN were accepted for inclusion. Whether by clinical exam, validated tool or nerve studies, diabetic neuropathy assessment should be explicitly reported for a study to be included.

Quality study appraisal

The quality of the included English studies was evaluated by the Joanna Briggs Institute critical appraisal tool for cross-sectional and case–control studies.[21] The quality assessment of the included studies written in Chinese language was reported from the study of Qu *et al.*[19]

Outcome definition

The primary outcome was set to be the serum level of vitamin D. Units were converted and reported in ng/ml. The secondary outcomes were defined as the prevalence of vitamin D insufficiency and the prevalence of vitamin D deficiency.

Data collection and extraction

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. An excel sheet was used to record all extracted data. Relevant data such as sample and patient characteristics, diabetes duration, types of comparison, BMI, fasting plasma glucose, HbA1c, tests used to detect and/or assess DN and laboratory methods for measuring vitamin D were recorded.

Data analysis

Statistical analysis was conducted using the software StatsDirect (Cambridge, UK). Two methods were used for mean comparison. First, an ANOVA was computed to look for significant differences between groups of comparison (diabetic patients with DN, without DN and in healthy subjects) when applicable. Then, an effect size MA using standardised mean difference (SMD) was conducted including those studies that reported their standard deviation values along with their mean values. An odds ratio MA was conducted to look for significant proportion differences related to the prevalence of vitamin D insufficiency and/or deficiency. Heterogeneity was assessed by the I^2 inconsistency test; random-effects estimate was reported whenever I^2 value exceeded 50 %. A P value <0·05 was considered as significant.

Results

Search results

The electronic search yielded ninety-four hit records, where six were duplicates. Forty-eight abstracts were excluded after initial checking. The remaining forty articles had their full manuscripts available for details. Sixteen were excluded for the following reasons: four studies reported outcomes of vitamin D supplementation to treat DN, six reviews, four lacked primary outcomes and two were irrelevant. Reference list checking of the twenty-four studies yielded another three relevant studies that fulfilled inclusion eligibility. In total, twenty-seven studies[1–8,10,11,13,22–35] met the inclusion criteria. Fig. 1 shows details of the search.

Study and pooled sample characteristic results

The total pooled sample included 6277 participants. All studies but one[10] reported the subgroup sample number where 2218 patients were diabetic with DN, 2959 were diabetic without DN and 406 healthy subjects. The mean age of the total sample was 53·7 ± 9·2 years. The mean diabetes duration was 10·2 ± 3·5 years. Table 1 shows the characteristics of the included studies.

Quality appraisal

Scores of the Joanna Briggs Institute tool for cross-sectional studies ranged between 5 and 8, out of a maximum value of 8 (Table 2).

Scores of the Joanna Briggs Institute tool for case–control studies ranged between 7 and 10, out of a maximum value of 10 (Table 3).

The quality of the Asian studies written in Chinese were not assessed in this review. However, those seven studies[27–30,33,34,35] were considered as having a moderate quality according to the Newcastle-Ottawa Scale.[19]

Outcomes

Table 4 summarises the outcomes of each included studies.

Mean serum vitamin D level. Twenty-five studies reported this outcome. Serum vitamin D values were 15·1 ± 4·2 ng/ml, 20·5 ± 6·4 ng/ml and 27·6 ± 8 ng/ml for diabetic patients with DN, without DN and in healthy subjects, respectively.

A two-way ANOVA analysis showed high significance between diabetic patients with and without DN ($P < 0·0001$) where those having DN showed significantly lesser values of serum vitamin D. When compared with healthy people, patients

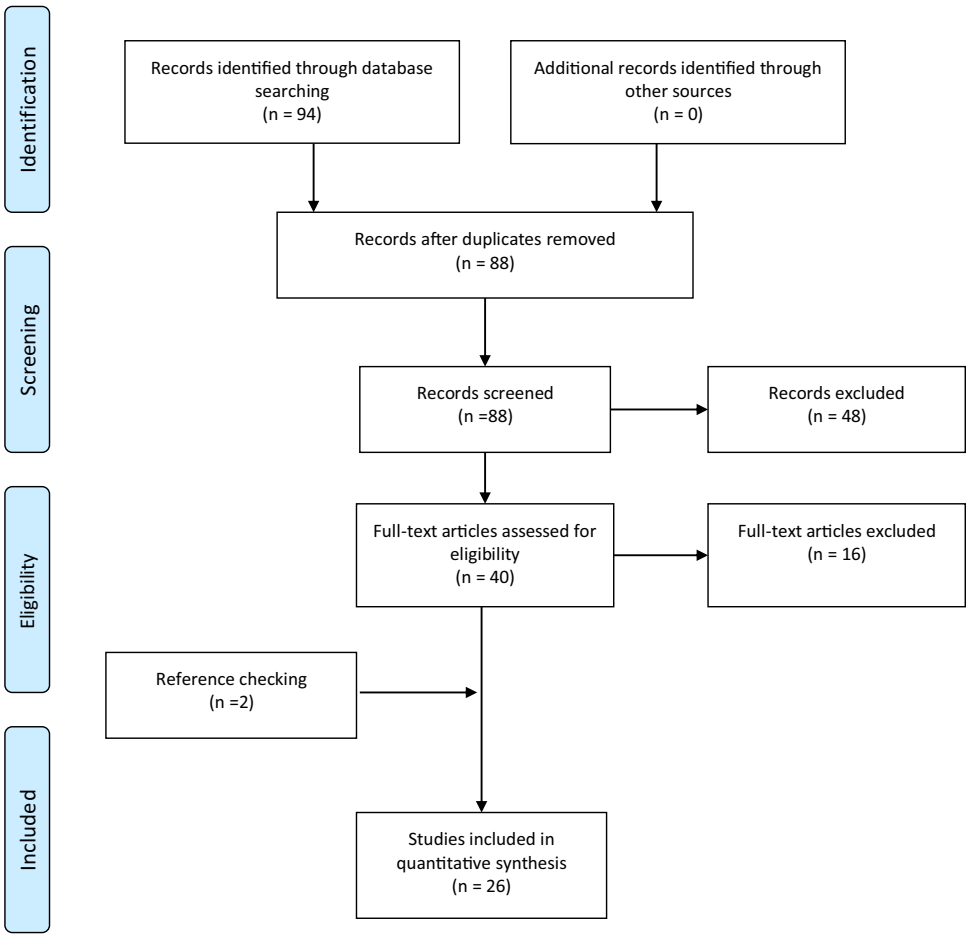

Fig. 1. PRISMA flow diagram.

with or without DN had significantly lesser values of serum vitamin D ($P < 0{\cdot}0001$, for both comparisons).

Similarly, when an effect size MA was conducted including twenty-five studies, it yielded a standardised mean difference of −0·92 (95 % CI −1·18, −0·65, $I^2 = 93{\cdot}3\,\%$, $P < 0{\cdot}0001$), significantly lesser serum Vitamin D values in diabetic patients with DN (Fig. 2).

Subgroup analysis based on race showed the following values: SMD of fifteen Caucasians studies was −0·81 (95 % CI −1·13, −0·49, $I^2 = 85{\cdot}4\,\%$, $P < 0{\cdot}0001$) and that of ten Asian studies was −1·04 (95 % CI −1·45, −0·59, $I^2 = 96{\cdot}6\,\%$, $P < 0{\cdot}0001$). Based on the study design, seven cross-sectional yielded an SMD of −0·48 (95 % CI −0·69, −0·26, $I^2 = 75{\cdot}8\,\%$, $P < 0{\cdot}0001$), and eighteen case–control yielded an SMD of −1·1 (95 % CI −1·47, −0·72, $I^2 = 93\,\%$, $P < 0{\cdot}0001$).

Prevalence of vitamin D insufficiency. Three studies[5,6,8] including 1996 diabetic patients with and without DN yielded a pooled OR of 0·84 (95 % CI 0·69, 1·04, $I^2 = 86{\cdot}4\,\%$, $P = 0{\cdot}1$). Non-significance was found for both models.

Prevalence of vitamin D deficiency. Four studies[5,8,25,32] including 1405 diabetic patients with and without DN yielded pooled OR of 1·84 (95 % CI 1·46, 2·33, $P < 0{\cdot}0001$) and 2·9 (95 % CI 1·10, 7·52, $P = 0{\cdot}03$) when using fixed-effects and random-effects models, respectively. For both models, the $I^2 = 91{\cdot}4\,\%$.

Prevalence of vitamin D insufficiency or deficiency. When combining insufficiency with deficiency with a total of 2076 diabetic patients with and without DN subjects, five studies yielded an OR of 2·8 (95 % CI 1·39, 5·79, $I^2 = 82{\cdot}9\,\%$, $P = 0{\cdot}004$).

Gender-based outcomes. Only Jung *et al.*[10] reported outcomes based on sex. The mean levels of 25(OH)D were significantly lower in patients with DN than in those without DN (12·7 ng/ml *v.* 18·7 ng/ml, $P = 0{\cdot}007$) and (9·3 ng/ml *v.* 13 ng/ml, $P = 0{\cdot}002$) in men and women, respectively.

Similarly, the prevalence of vitamin D deficiency was significantly higher in men and women with DN than in those without DN.

Discussion

The aim of the present MA was to explore the association between diabetic neuropathy and vitamin D levels in patients with type 2 diabetes. Diabetic neuropathy is one of the many complications that develop with diabetes and among the major

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Table 1. Characteristics of included studies

Studies	Study type	Total sample	DM with DN sample	DM without DN sample	Healthy sample	Age (years)	Diabetic duration (years)	Tests used for DN	Measurement method of vitamin D
Yoho et al, 2009	Prospective case–control	41	13	13	15	59 ± 9	NR	PE + MFT	NR
Chaychi *et al.*, 2011	Retrospective case–control	22	11	11	NR	58 ± 8	NR	MNSI + NCS	LC/MS
Skalli *et al.*, 2011	Cross-sectional	111	62	49	NR	71 ± 11	DM with DN: 18 ± 10 DM DM with DN: 12 DN: 10 ± 7	PE + MFT	RIA
Shehab *et al.*, 2012	Cross-sectional	210	87	123	NR	DM with DN: 58 ± 10 DM without DN: 59 ± 11	75 subjects >10 135 subjects <10	NSS + NDS + NCS+	RIA
Soderstrom *et al.*, 2012	Cross-sectional	591	287	304	NR	> 40	NR	PE + MFT	ECLIA
Ahmadieh *et al.*, 2013	Cross-sectional	210	86	50	74	59	8·6	UKSS + ISL	RIA
Bajaj *et al.*, 2014	Retrospective case–control	288	56	102	130	53 ± 8	5 ± 3	PE + NCS	NR
Xiao LF *et al.*, 2014	Case–control	146	76	70	NR	NR	NR	NR	ECLIA
Zhang JP *et al.*, 2014	Cross-sectional	80	37	43	NR	NR	NR	NR	ECLIA
Kheyami et al., 2014	Prospective case–control	81	12	43	26	Healthy Control: 40 ± 16 without DN: 43 ± 13 With DN: 52 ± 16	NR	PE + NCS	ELISA
Alamdari *et al.*, 2015	Prospective case–control	62	33	29	NR	DM with DN: 53·9 DM without DN: 56·6	DM with DN: 7·7 DM without DN 9·2	NCS	RIA
Celikbilek *et al.*, 2015	Prospective case–control	118	24	25	69	Healthy Control: 59 ± 11 DM without DN: 56 ± 10	NR	NCS	ELISA
Jung *et al.*, 2015	Cross-sectional	257	NR	NR	NR	59 ± 2	8 ± 8	EP + MNSI + MFT	RIDK
Wang YF *et al.*, 2015	Retrospective case–control	120	60	60	NR	NR	NR	NR	ECLIA
Cui *et al.*, 2015[a]	Retrospective case–control	200	89	111	NR	NR	NR	NR	ECLIA
Cui *et al.*, 2015[b]	Retrospective case–control	200	107	93	NR	NR	NR	NR	ECLIA
Wang Q *et al.*, 2016	Prospective case–control	230	123	107	NR	NR	NR	NR	ECLIA
Wang N *et al.*, 2016	Prospective case–control	101	52	49	NR	NR	NR	NR	NR
Bilir *et al.*, 2016	Prospective case–control	103	37	33	33	NR	NR	EP	UPLC
Ozuguz *et al.*, 2016	Cross-sectional	96	26	70	NR	DM with DN: 38 ± 12 DM without DN: 28 ± 9	DM with DN: 18 ± 8 DM without DN: 11 ± 6	EP + MNSI + MFT	RIA
He *et al.*, 2017	Cross-sectional	861	527	334	NR	DM with DN: 65·77 ± 9·31 DM without DN: 57 ± 11	DM with DN: 12 ± 7 DM without DN: 8·55 ± 5·98	PE + EMG	ECLIA
Zambelis *et al.*, 2017 (Greek)	Prospective case–control	101	59	42	NR	49·18	7 ±6	NSS + NDS + NCS + QST	ECLIA
Zambelis *et al.*, 2017 (Bangladeshi)	Prospective case–control	111	53	58	NR	47·35	6 ± 5	NSS + NDS + NCS + QST	ECLIA
	Prospective case–control	80	40	20	20		9 ± 5	NDS + NCS	EIA

Table 1. (*Continued*)

Studies	Study type	Total sample	DM with DN sample	DM without DN sample	Healthy sample	Age (years)	Diabetic duration (years)	Tests used for DN	Measurement method of vitamin D
Abdelsadek *et al.*, 2018						Healthy control: 46 ± 2 DM without DN: 47 ± 4			
Fan *et al.*, 2018	Prospective case–control	287	164	123	NR	59·7 ± 10.·3	8 ± 7	PE	ELISA
Shillo *et al.*, 2019	Prospective case–control	59	31	14	14	NR	NR	DN4+ NIS(LL) + NCS	ECLIA
Niu *et al.*, 2019	Cross-sectional	1461	478	983	NR	61 ± 12	DM with DN: 12 DM without DN: 8	NR	ECLIA

DM, diabetes mellitus; DN, diabetic neuropathy; DN4, Douleur neuropathique-4; DNES, diabetic neuropathy examination score; EIA, enzyme immunoassays; ELISA, enzyme-linked immunosorbent assay; ECLIA, electrochemiluminescence immunoassay; EP, electrophysiological; LC/MS, liquid chromatography-mass spectrometry; MFT, monofilament test; MNSI, Michigan neuropathy screening instrument; NCS, nerve conduction studies; NDS, neuropathy disability score; NIS (LL), neuropathy impairment score lower limb; NR, not reported; NSS, neuropathy symptom score; PE, physical examination; QNE, quantitative neurological examination; QST, quantitative sensory test; RIA, radioimmunoassay; RIDK, radio immunologic determination kit; UKSS, UK screening score; UPLC, ultra-performance liquid chromatography.

Table 2. Joanna Briggs institute critical appraisal checklist for cross-sectional studies

Items	Skalli *et al.*, 2011	Shehab *et al.*, 2012	Soderstrom *et al.*, 2012	Ahmadieh *et al.*, 2013	Jung *et al.*, 2015	Ozuguz *et al.*, 2016	He *et al.*, 2017	Niu *et al.*, 2019
1. Were the criteria for inclusion in the sample clearly defined?	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
2. Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were objective, standard criteria used for measurement of the condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were confounding factors identified?	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
6. Were strategies to deal with confounding factors stated?	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
7. Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total of ''Yes''	5	8	8	7	8	6	8	8

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Table 3. Joanna Briggs institute critical appraisal checklist for case–control studies

Checklist	Yoho et al., 2009	Chaychi et al., 2011	Bajaj et al., 2014	Kheyami et al., 2014	Celikbilek et al., 2015	Alamdari et al., 2015	Celikbilek et al., 2015	Bilir et al., 2016	AbdelSadek, 2018	Zambelis et al., 2017	Abdelsadek et al., 2018	Fan et al., 2018	Shillo et al., 2019
9. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were cases and controls matched appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the same criteria used for identification of cases and controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes
12. Was exposure measured in a standard, valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was exposure measured in the same way for cases and controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Were confounding factors identified?	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	No	Yes	Unclear	Unclear	Unclear	Yes
15. Were strategies to deal with confounding factors stated?	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes
16. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Was the exposure period of interest long enough to be meaningful?	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear
18. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total of "Yes"	9	8	8	7	7	9	9	7	10	7	8	7	9

causes of death in this population.[20] Thus, it is crucial to identify its risk factors. The present MA included twenty-six studies with a total sample size of 6277 participants; mean age of 53·7 (SD = 9·2) and mean diabetes duration of 10·2 years (SD = 3·5). The findings indicated a statistical significance between serum levels of vitamin D and diabetic neuropathy.

Main findings

Results showed that patients with neuropathy had significantly lower levels of serum vitamin D compared with those without neuropathy. Moreover, patients with diabetic neuropathy had 1·84 and 2·87 higher odds of being deficient in vitamin D using both fixed and random effect models, respectively. Subgroup analyses of vitamin D serum level showed similar significance; results were not affected by race or study design. The prevalence of vitamin D insufficiency among diabetic neuropathy patients was assessed in 1996 patients but with non-significant differences. When combining both outcomes, deficiency and insufficiency, patients with diabetic neuropathy had 2·8 higher odds of being deficient/insufficient in vitamin D.

Interpretation of the results

The findings are in line with previously published meta-analyses that have proven the association between vitamin D deficiency and diabetic neuropathy.[18] However, our MA differs considerably given that: a) twenty-six studies were included (*v.* 6 to 13)[18–20], b) our sample size was considerably larger (6277 *v.* sample sizes below 3000) and c) our weighted SMD was the highest, which gives higher evidence towards an association between vitamin D and DN. Though a correlation could not be stated, the association seem to be very high and warrants future large-sampled prospective trials.

Regarding vitamin D insufficiency, it is important to note that there is a lack of consensus regarding the threshold in the literature. As such, to address this ambiguity pooled insufficiency, data analyses were conducted to examine its association with diabetic neuropathy. The low statistical significance may be due to the lack of consensus for cut-off values for defining vitamin D levels. Indeed, cut-off points to define vitamin D deficiency, insufficiency, sufficiency and intoxication vary considerably among studies. For example, vitamin D deficiency may be set at levels below 20 ng/ml or 10 ng/ml (e.g.[10,36]) and insufficiency at 20–29 ng/ml or below 24 ng/ml depending on the studies.[14,37] Some authors suggested the importance of the parathyroid hormone (PTH) as a functional measure for assessing the 'adequacy' for serum vitamin D.[38] Taking into consideration that an optimum level of 25(OH) D is required to suppress PTH activity, results from cross-sectional examinations revealed a value of 30 ng/ml vitamin D as adequate. However, this was only a representation of an average value of the population and did not reflect the variation of vitamin D adequacy for individuals.[38] This suggests that more studies are needed to determine official cut-offs that can be used globally to determine Vitamin D deficiency, insufficiency and sufficiency.

The predominance of vitamin D deficiency and insufficiency was assessed among diabetic neuropathy patients using five

Table 4. Primary and secondary outcomes

Studies	Mean 25(OH)D in diabetic subjects with DN (ng/ml)	Mean 25(OH)D in diabetic subjects w/out DN (ng/ml)	Mean 25(OH) D in healthy subjects (ng/ml)	Prevalence vitamin D insufficiency with DN	Prevalence vitamin D insufficiency w/out DN	Prevalence vitamin D deficiency with DN	Prevalence vitamin D deficiency w/out DN	Normal (sufficient) level of 25(OH)D (ng/ml)	Cut-off value for 25(OH)D deficiency (ng/ml)	Cut-off value for 25(OH)D insufficiency (ng/ml)
Yoho *et al.*, 2009	14 ± 5	17 ± 8	27 ± 9	NR	NR	NR	NR	>30	<10	10–30
Chaychi *et al.*, 2011	21 ± 9	36 ± 7·5	NR	NR	NR	NR	NR	NR	NR	NR
Skalli *et al.*, 2011	10 ± 5	14 ± 7	NR	NR	NR	NR	NR	NR	NR	NR
Shehab *et al.*, 2012	15 ± 16	23 ± 24	NR	NR	NR	NR	NR	NR	NR	NR
Soderstrom *et al.*, 2012	NR	NR	NR	243 (85·5 %)	234 (77.0%)	NR	NR	>30	NR	<30
Ahmadieh *et al.*, 2013	16 ± 10	23·5 ± 14·5	22.5 ± 12	NR	NR	NR	NR	NR	NR	NR
Bajaj *et al.*, 2014	17 ± 4	23 ± 6	NR	NR	NR	43 (76·8 %)	147 (51·2 %)	>30	<20	20–29
Xiao LF *et al.*, 2014	12 ± 4	24 ± 6	NR	NR	NR	NR	NR	NR	NR	NR
Zhang JP *et al.*, 2014	13 ± 5	18 ± 5	NR	NR	NR	NR	NR	NR	NR	NR
Kheyami *et al.*, 2014	23 ± 5	29 ± 2·5	22 ± 4	NR	NR	NR	NR	NR	NR	NR
Alamdari *et al.*, 2015	13·5 ± 5	21 ± 11·5	NR	NR	NR	NR	NR	NR	NR	NR
Celikbilek *et al.*, 2015	23 ± 8	33 ± 7	43 ± 9	NR	NR	NR	NR	NR	NR	NR
Jung *et al.*, 2015 (111 males)	12·7	18·7	NR	7/60 (11·6 %)	NR	9/21 (42·8 %)	NR	>20	<10	10–20
Jung *et al.*, 2015 (146 females)	9·3	13	NR	26/72 (36 %)	NR	17/63 (27 %)	NR	NR	NR	NR
Wang YF *et al.*, 2015	12 ± 4	24 ± 6	NR	NR	NR	NR	NR	NR	NR	NR
Cui *et al.*, 2015	15 ± 3	23 ± 4	NR	NR	NR	NR	NR	NR	NR	NR
Cui *et al.*, 2015 (for elderly)	16 ± 9·5	22 ± 10	NR	NR	NR	NR	NR	NR	NR	NR
Wang Q *et al.*, 2016	9 ± 4	12 ± 6	NR	NR	NR	NR	NR	NR	NR	NR
Wang N *et al.*, 2016	12 ± 6	15 ± 6	NR	NR	NR	NR	NR	NR	NR	NR
Bilir *et al.*, 2016	10 ± 5	14 ± 6	18 ± 3·5	NR	NR	NR	NR	NR	NR	NR
Ozuguz *et al.*, 2016	11 ± 5	13.5 ± 5	NR	NR	NR	NR	NR	NR	NR	NR
He *et al.*, 2017	16 ± 8	18 ± 7	NR	141	109 (32·6 %)	354	206 (61·7 %)	>30	<20	21–29
Zambelis *et al.*, 2017 (Greek)	23 ± 12	19 ± 12	NR	NR	NR	NR	NR	NR	NR	NR
Zambelis *et al.*, 2017 (Bangladeshi)	12 ± 6	11 ± 5	NR	NR	NR	NR	NR	NR	NR	NR
Abdelsadek *et al.*, 2018	21 ± 8	31 ± 15	30 ± 10	NR	NR	35 (87·6 %)	9 (45 %)	>30	<20	21–29
Fan *et al.*, 2018	16 ± 4	19 ± 5	NR	29 (17·7 %)	48 (39 %)	135 (82·3 %)	70 (56·9 %)	30–60	<20	20–30
Shillo *et al.*, 2019	14 ± 2	20 ± 2	25 ± 3	NR	NR	NR	NR	NR	NR	NR
Nui *et al.*, 2019	17 ± 8	18 ± 7	NR	NR	NR	NR	NR	NR	NR	NR

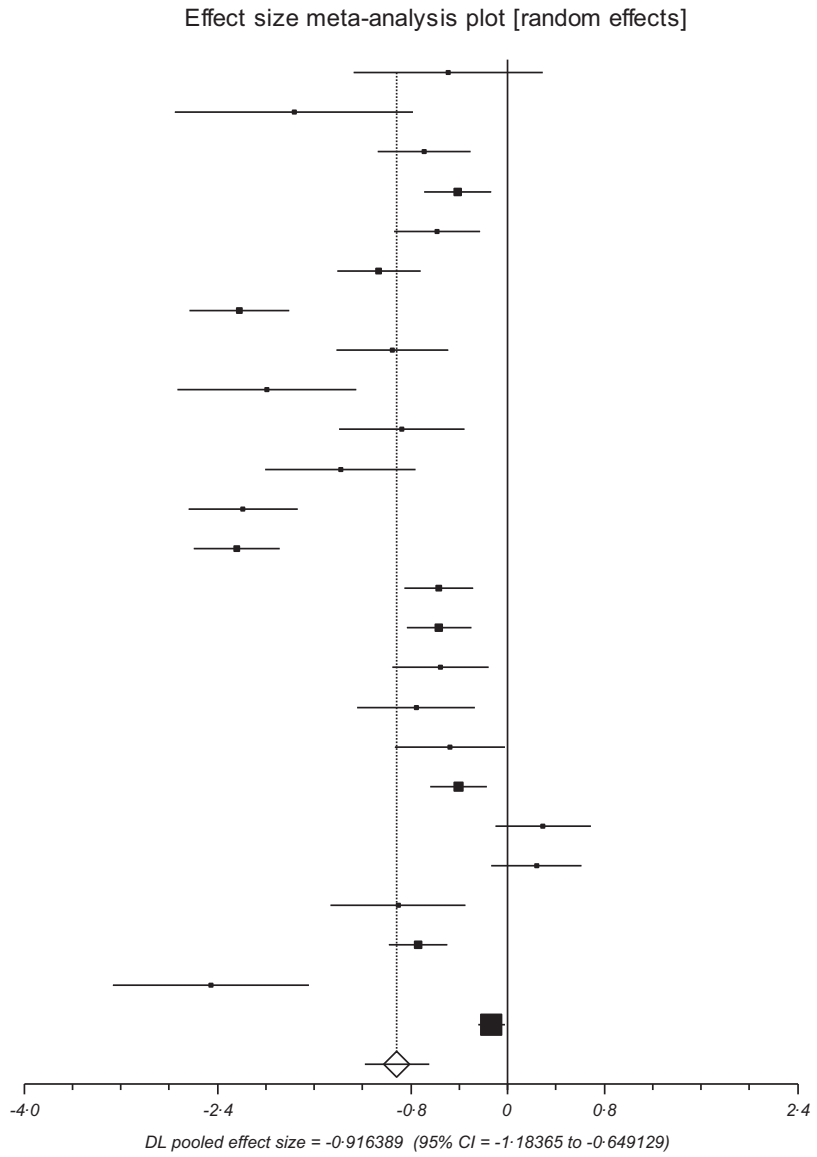

Fig. 2. Forest plot of main finding.

studies with a sample size of 2076. The purpose of assessing both deficiency and insufficiency was to capture the gap between the values of deficiency and insufficiency found among most studies. Again, our results point out to the necessity of more reliable cut-off values to differentiate between deficiency, insufficiency and sufficiency. Two very recent studies were located at the completion of our review; Darraj *et al.*[39] reported a vitamin D deficit prevalence of 60·8 % among patients with diabetes, and Senyigit[40] demonstrated that diabetic patients with DN had significant lower levels than those without the neuropathy.

Vitamin D role in diabetes and diabetic neuropathy

Previous work has shown that diabetic neuropathy is associated with decreased nerve growth factor (NGF) expression in human diabetic nerves and that exogenous NGF can reverse some of the pathological changes in diabetic nerves.[41–43] In parallel, vitamin D is known to induce NGF synthesis in human cell lines.[44] Therefore, vitamin D may protect diabetic patients from neuropathy through its enhancement of NGF synthesis. In fact, in an experiment on streptozotocin-diabetic rats, a vitamin D_3 derivative induced NGF synthesis and prevented neurotrophic deficits.[45]

In addition, vitamin D supplementation was previously shown to result in a significant improvement in neuropathic pain management in diabetic patients[3] as well as a reduction in neuropathy symptom scores.[2] Similarly, a number of clinical trials have linked vitamin D supplementation with the improvement of both pain and neuropathy-specific quality of life in diabetic patients concluding that vitamin D is an independent risk factor for the presence and severity of diabetic neuropathy.[4]

Recent published work has also suggested that vitamin D deficiency may play a role in the pathogenesis of small-fibre neuropathy particularly affecting nociceptor fibres.[22] Other studies proposed that the association between vitamin D deficiency and neuropathy stems from the pathogenesis of type 2

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diabetes through β-cell function, insulin secretion and plasma calcium levels. In that context, vitamin D supplementation was shown to cause an increase in serum Ca, a reduction in serum free fatty acids, higher insulin secretion as well as better glucose tolerance.[2] These findings and mechanisms suggest the importance of vitamin D levels when assessing diabetic neuropathy as well as the effect of vitamin D on the control of insulin in diabetic patients.

Limitations

The present MA does have some potential limitations. First, severe heterogeneity was observed between included articles, and sensitivity analysis found that one article made a great influence on this MA. Second, some included articles were small sampled; however, the pooled sample of 6277 participants could be considered as a fair representative of the population. Larger prospective comparative studies are needed to support our findings. Third, the definition of DPN was not uniform due to a variety of different measurements of DPN and that might have impacted our results. Fourth, different methods were used to assess peripheral neuropathy. Fifth, grey literature was not searched with the possibility of missing relevant unpublished articles, conference abstracts or public reports. Sixth, other potential confounding factors that were not investigated and reported in the included studies (season variations at the time of measurement, levels of sun exposure and populations of different ethnicities) could have introduced bias to the true association between vitamin D level and DPN. Though we conducted two subgroup analyses, one based on race and the other based on study design, heterogeneity was still too high. Selection bias could be one cause of such heterogeneity, despite the fact that quality scores ranged from good to excellent.

Conclusion

In conclusion, the available literature exhibits that vitamin D deficiency could be used as a predictor of diabetic peripheral neuropathy in older adults. However, despite the validation of the studies used in this MA, more randomised controlled trials and prospective studies as well as studies testing the optimum serum vitamin D for normal functioning should be conducted. These additional studies are necessary to understand the mechanism directly linking vitamin D to diabetic neuropathy and to set recommendations for vitamin D supplementation in order to prevent or slow down the development of DPN in diabetic patients.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Author contributions

The study was designed by KY. Each author equally contributed to the literature search and data extraction. Data analysis was completed by KY. All authors contributed to the interpretation of the results and the manuscript draft which then was approved by all.

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