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EFFECT OF VITAMIN D SUPPLEMENTATION ON GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Background & Purpose: Vitamin D level in plasma has been connected to the occurrence of metabolic syndrome and insulin resistance. The Aim of this work is to provide cumulative data about the effect of vitamin D supplementation on glycemic control in type 2 Diabetes Mellitus (DM) patients. ***Methods:*** A systematic search was performed of PubMed, Cochrane library Ovid, Scopus & Google scholar to identify Endocrinology RCTs, clinical trials, and comparative studies, which studied the outcome of Vitamin D group versus Placebo group of DM patients. A meta-analysis was done using fixed and random-effect methods. The primary outcome was the mean change from baseline in serum vitamin D. Secondary outcome was the effects on HbA1c. ***Results:*** A total of 5 studies were identified involving 245 patients, with 138 patients in Vitamin D group, and 107 patients in Placebo group. Regarding primary outcome measures, the fixed-effects model of the meta- analysis study showed highly significant increase in mean vitamin D change in Vitamin D supplemented group compared to Placebo group (p =

0.049). Regarding secondary outcome measures, the fixed-effects model of the meta-analysis study showed non-significant difference in vitamin D effects on HbA1c in Vitamin D supplemented group compared to Placebo group ($p > 0.05$). ***Conclusion:*** To conclude, current evidence of RCTs does now not support short-term vitamin D supplementation in a heterogeneous population with type 2 diabetes. however, in patients with poorly controlled diabetes, a favorable effect of vitamin D is seen on fasting glucose.

KEYWORDS: Vitamin D, Glycemic control, DM.

INTRODUCTION

Vitamin D is a key element for the renovation of calcium and bone homeostasis. over the last decade, vitamin D has attracted substantial interest because of its extra-skeletal roles in numerous disease conditions, including diabetes mellitus. This interest has arisen due to the identification that maximum cells, which includes the pancreatic beta-cells, contain the vitamin D receptor (VDR). Most of those cells additionally have the capability to produce the biologically active form of vitamin D: 1, 25-dihydroxyvitamin D for paracrine functions. furthermore, vitamin D is known to have immuno-modulatory and anti-inflammatory effects, which could enhance peripheral insulin resistance by way of changing low-grade chronic infection that has been implicated in insulin resistance in type 2 diabetes mellitus.[1]

Previous scientific studies have established an association of suboptimal vitamin D status with increased all-cause and cardiovascular mortality, coronary heart disease and various cardiovascular risk factors such as hypertension and metabolic syndrome. Currently, there is no universally accepted definition of optimal vitamin D level and the prevalence of vitamin D deficiency was likely underestimated. With serum 25-hydroxyvitamin D [25(OH)D] taken into consideration because the best indicator of vitamin D status, most experts recommend an optimal level of 25(OH)D > 30ng/mL and define vitamin D deficiency and insufficiency as serum 25(OH)D < 20 ng/mL and 21-29 ng/mL, respectively.[2]

Vitamin D insufficiency and deficiency are being increasingly identified world-wide. Serum 25 (OH) D ranges have even been related to mortality inside the general population. Vitamin D level in plasma has been connected to the occurrence of metabolic syndrome and insulin resistance. Though epidemiological studies demonstrate an association between low serum 25(OH) vitamin D and glucose intolerance, intervention trials using vitamin D have produced mixed outcomes.[3]

Low 25-hydroxyvitamin D (25(OH) D) levels are highly regularly occurring among type 2 diabetic patients. The association between vitamin D and type 2 diabetes may be explained by using the results of vitamin D at the regulation of insulin secretion or sensitivity or the attenuation of systemic inflammation.[4]

Aim of the study: The Aim of this work is to provide cumulative data about the effect of vitamin D supplementation on glycemic control in type 2 Diabetes Mellitus (DM) patients.

METHODS

This review was carried out using the standard methods mentioned within the Cochrane handbook and in accordance with the (PRISMA) statement guidelines.[5]

Identification of studies

- An initial search carried out throughout the PubMed, Cochrane library Ovid, Scopus & Google scholar using the following keywords: Vitamin D, Glycemic control, DM.
- We will consider published, full text studies in English only. Moreover, no attempts were made to locate any unpublished studies nor non-English studies.

Criteria of accepted studies

- **Types of studies**

The review will be restricted to RCTs, clinical trials, and comparative studies, either prospective or retrospective, which studied the outcome of Vitamin D group versus Placebo group of DM patients.

- Types of participants: Participants will be DM patients.

- Types of outcome measures:

1. Mean vitamin D change from baseline (1ry outcome)
2. Vitamin D effects on HbA1c (2ry outcome)

Inclusion criteria

- ✓ English literature.
- ✓ Journal articles.
- ✓ Between 2008 until 2016.
- ✓ Describing DM patients received either Vitamin D group or Placebo group.
- ✓ Human studies.

Exclusion criteria

- ✓ Articles describing other types of DM (e.g. type-1 DM).
- ✓ Irrelevance to our study.

Methods of the review

- **Locating studies**

Abstracts of articles identified using the above search strategy will be viewed, and articles that appear of fulfill our inclusion criteria will be retrieved in full, when there is a doubt, a second reviewer will assess the article and consensus will be reached.

- **Data extraction**

Using the following keywords: Vitamin D, Glycemic control, DM, data will be independently extracted by two reviewers and cross-checked.

Statistical analysis

Statistical analysis done using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Data were pooled and odds ratios (ORs) as well as standard mean differences (SMD), were calculated with their 95 per cent confidence intervals (CI). A meta-analysis was performed to calculate direct estimates of each treatment, technique or outcome. According to heterogeneity across trials using the I^2-statistics; a fixed- effect model ($P \geq 0.1$) or random-effects model ($P < 0.1$) was used.

Study selection

We found 140 records; 95 were excluded based on title and abstract review; 45 articles are searched for eligibility by full text review; 19 articles cannot be accessed or obtain full text; 10 studies were reviews and case reports; 11 were not describing functional outcome; leaving 5 studies that met all inclusion criteria (Fig. 1).

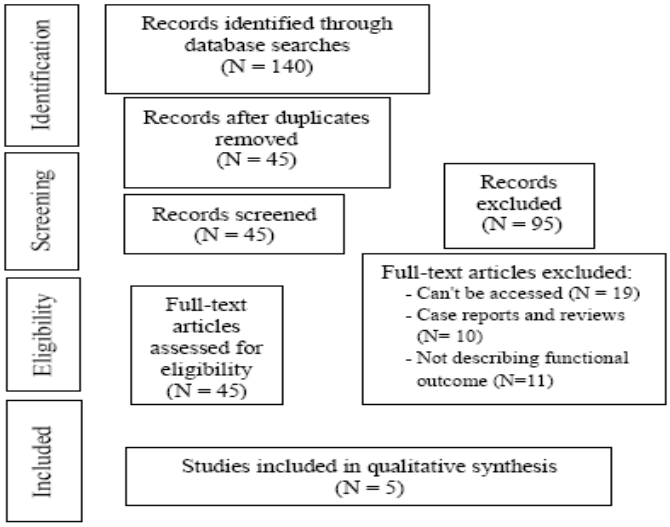

Figure 1: Flow chart for study selection.

RESULTS

Descriptive analysis of all studies included (Tables 1, 2)

Table 1: Patients and study characteristics.

N	Author	Total	Number of patients Vitamin D group	Placebo group	Age (average years)	Follow up time (average months)
1	***Sugden et al., 2008***	34	17	17	64	2
2	***Breslavsky et al., 2013***	47	24	23	66	12
3	***Kampmann et al., 2014***	15	7	8	59	3
4	***Nikooyeh et al., 2014***	90	60	30	45	3
5	***Jafari et al., 2016***	59	30	29	57	3

#Studies were arranged according to publication year.

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcome			Secondary outcome		
		Mean vitamin D change (towards vit D group)			Vitamin D effects on HbA1c (towards vit D group)		
		Mean change (nmol/L)	Lower limit	Upper limit	Mean change (%)	Lower limit	Upper limit
1	***Sugden et al., 2008***	15.3	5.42	25.18	-0.12	-0.79	0.55
2	***Breslavsky et al., 2013***	8.7	-4.36	21.76	-0.42	-1	0.16
3	***Kampmann et al., 2014***	76.5	38.35	114.65	---	---	---
4	***Nikooyeh et al., 2014***	37.7	22.56	52.84	0.9	0.44	1.35
5	***Jafari et al., 2016***	31.9	19.62	42.76	0.3	-0.21	0.81

The included studies published between 2008 and 2016.

Regarding patients' characteristics, the total number of patients in all the included studies was 245 patients, with 138 patients in Vitamin D group, and 107 patients in Placebo group, while their average follow up time was (4.5 months). The average age of all patients was (58 years).

Meta-analysis of outcome measures

Data were divided into two groups:

1) Vitamin D group
2) Placebo group

Meta-analysis study was done on 5 studies which described and compared the 2 different groups of patients; with overall number of patients (N=245).

Patients who achieved outcome measures were pooled:

Each outcome was measured by

✓ **Standard Mean Difference (SMD)**

- For mean vitamin D change.
- For vitamin D effects on HbA1c.

Regarding primary outcome measure,

We found 5 studies reported mean vitamin D change with total number of patients (N=245). I^2 (inconsistency) was 0% with non-significant Q test for heterogeneity ($p > 0.05$), so fixed-effects model was carried out; with overall SMD= 23.16 (95% CI -0.0058 to 46.3).

The fixed-effects model of the meta-analysis study showed highly significant increase in mean vitamin D change in Vitamin D supplemented group compared to Placebo group ($p = 0.049$).

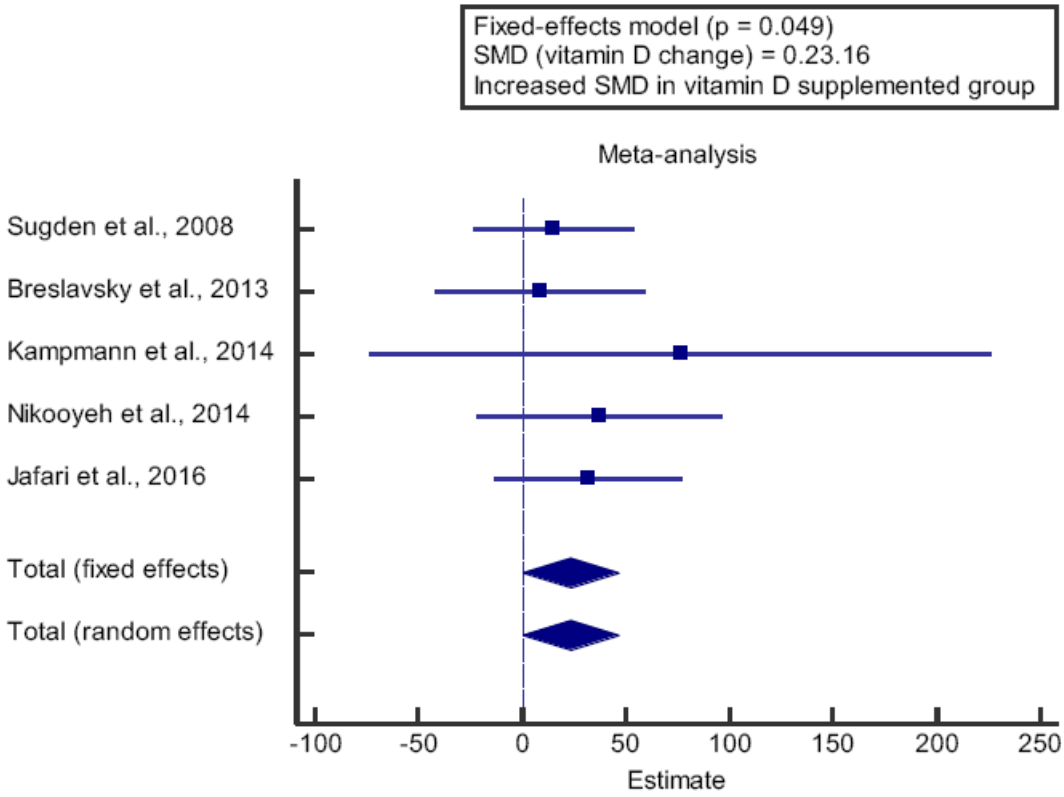

Figure 2: Forest plot of (mean vitamin D change) on Vitamin D group vs Placebo group – Mean difference.

Regarding secondary outcome measure,

We found 4 studies reported vitamin D effects on HbA1c with total number of patients (N=230).

I^2 (inconsistency) was 0% with non-significant Q test for heterogeneity ($p > 0.05$), so fixed-effects model was carried out; with overall SMD= 0.28 (95% CI -0.76 to 1.34).

The fixed-effects model of the meta-analysis study showed non-significant difference in vitamin D effects on HbA1c in Vitamin D supplemented group compared to Placebo group ($p > 0.05$).

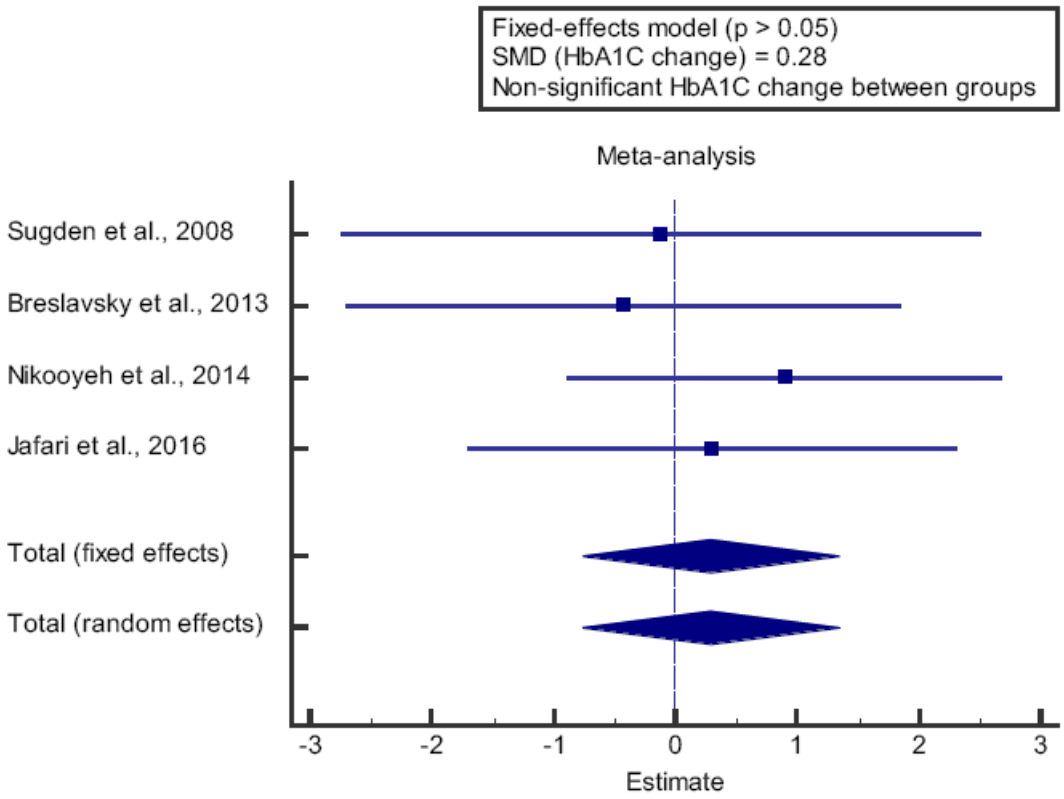

Figure 3: Forest plot of (vitamin D effects on HbA1c) on Vitamin D group vs Placebo group – Mean difference.

DISCUSSION

The Aim of this work is to provide cumulative data about the effect of vitamin D supplementation on glycemic control in type 2 Diabetes Mellitus (DM) patients.

The included studies published between 2008 and 2016.

Regarding patients' characteristics, the total number of patients in all the included studies was 245 patients, with 138 patients in Vitamin D group, and 107 patients in Placebo group, while their average follow up time was (4.5 months). The average age of all patients was (58 years).

Meta-analysis of outcome measures; Data were divided into two groups **(Vitamin D group and Placebo group).**

Meta-analysis study was done on 5 studies which described and compared the 2 different groups of patients; with overall number of patients (N=245).

Regarding primary outcome measure; we found 5 studies reported mean vitamin D change

with total number of patients (N=245).

The fixed-effects model of the meta-analysis study showed highly significant increase in mean vitamin D change in Vitamin D supplemented group compared to Placebo group (p = 0.049) which came in agreement with ***Sadiya et al. 2015***[6] and with ***Moreira-Lucas et al. 2017***.[7]

Sadiya et al. 2015.[6] reported that After supplementation, serum 25(OH) D peaked in the vitamin D-group in phase 1 (77.2 ± 30.1 nmol/l, P = 0.003) followed by a decrease in the phase 2 (61.4 ± 18.8 nmol/l, P = 0.006), despite the fact that this was higher compared with baseline. In the placebo group, no distinction become found in the serum 25(OH) D ranges all through the intervention.

Moreira-Lucas et al. 2017[7] reported that Mean baseline serum 25(OH) D was 48.1 and 47.6 nmol/L in the VitD and placebo groups, respectively. Serum level 25(OH) D significantly increased to 98.7 nmol/L (51 nmol/L increase; P< 0.0001) in the VitD group.

Regarding secondary outcome measure; we found 4 studies reported vitamin D effects on HbA1c with total number of patients (N=230).

The fixed-effects model of the meta-analysis study showed non-significant difference in vitamin D effects on HbA1c in Vitamin D supplemented group compared to Placebo group (p > 0.05) which came in agreement with ***Krul-Poel et al. 2017***[1] and with ***Krul-Poel et al. 2015***[8] and disagreement with ***Wu et al. 2017.***[4]

Krul-Poel et al. 2017[1] reported that Nineteen researches included HbA_{1c} as outcome variable. Combining these researches, no significant effect in change of HbA_{1c} was seen after vitamin D intervention compared with placebo.

Krul-Poel et al. 2015[8] reported that mean baseline HbA1c was 6.8 ± 0.5% (51 ± 6 mmol/mol) in each groups. After 6 months, no effect was seen on HbA1c (mean distinction: β = 0.4; P = 0.42) and other signs of glycemic control (HOMA of insulin resistance, fasting insulin, and glucose) in the entire study population.

Wu et al. 2017[4] reported that Significantly reduced HbA1c levels were also observed to be in relation to vitamin D supplementation in the subgroup including type 2 diabetes patients

with a body mass index (BMI)< 30 kg m−2 (SMD −0.30).

CONCLUSION

To conclude, current evidence of RCTs does now not support short-term vitamin D supplementation in a heterogeneous population with type 2 diabetes. However, in patients with poorly controlled diabetes, a favorable effect of vitamin D is seen on fasting glucose.

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Conflict of interest

None.

Authorship

All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

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