

The Analysis Study of The Effect Vitamin D to Risk for Type 2 Diabetes Mellitus in People with Pre-Diabetes : A Comprehensive Systematic Review

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Article History :

Received date : 2024/04/08
Revised date : 2024/05/19
Accepted date : 2024/07/25
Published date : 2024/09/02



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E-ISSN :

ISSN 3048-1368



P-ISSN :

ISSN 3048-1376



ABSTRACT

Background: Individuals with prediabetes are at a 50% increased risk of advancing to Type 2 Diabetes Mellitus (T2DM). Deficient levels of vitamin D are associated with higher risks of insulin resistance and diabetes. **Methods:** This systematic review adhered to PRISMA 2020 guidelines, focusing exclusively on full-text articles published in English between 2012 and 2024. **Result:** The review process involved analyzing over 300 publications from the selected databases. After an initial screening, eight studies met the criteria for detailed examination. These studies underwent an in-depth review to ensure a rigorous and comprehensive evaluation of their findings. **Conclusion:** Vitamin D supplementation may offer potential benefits in reducing the risk of T2DM in individuals with prediabetes by enhancing insulin synthesis and sensitivity. However, the overall effectiveness of diabetes prevention is still debated, with recent large-scale trials reporting nonsignificant results. The fat-soluble nature of vitamin D may limit its effectiveness in obese individuals. The American Diabetes Association advocates for further research to explore the potential advantages of combining vitamin D supplementation with lifestyle interventions.

Keyword: vitamin D, prediabetes, diabetes, insulin resistance

INTRODUCTION

Diabetes affects over 400 million people worldwide.¹ Prediabetes is characterized by elevated fasting glucose or impaired glucose tolerance in individuals who do not yet meet the criteria for diabetes.² In 2017, the International Diabetes Federation (IDF) estimated that approximately 374 million adults had prediabetes, representing a prevalence rate of 7.7%.³ Those with prediabetes face a 50% higher risk of progressing to type 2 diabetes.⁴ Diabetes mellitus is associated with severe complications, including stroke, cardiovascular disease, and neuropathy, affecting both vascular and nonvascular systems. Therefore, implementing effective strategies to prevent the progression from prediabetes to diabetes is essential.⁵

Vitamin D, a seco-steroid hormone, is well-known for its role in bone and musculoskeletal health by enhancing calcium absorption in the intestines.⁶ Beyond its skeletal benefits, vitamin D is implicated in various extra-skeletal effects,

including influences on cardiovascular health, cancer risk, diabetes, and immune responses.⁷ The primary source of vitamin D is skin synthesis, triggered by exposure to ultraviolet B (UVB) radiation, though dietary sources are limited and infrequently consumed. Despite a significant rate of vitamin D supplementation (85%), deficiency (<30 nmol/L) affects 1 in 8 Irish adults aged 50 and older, with prevalence rising to nearly 1 in 2 among those over 85 years.⁸

In diabetes pathogenesis, vitamin D appears to play a crucial role in glucose regulation. It facilitates insulin secretion by enabling pancreatic beta cells to convert inactive vitamin D into its active form and influences the expression of genes involved in insulin signaling.⁹⁻¹¹ Low vitamin D levels are hypothesized to increase the risk of insulin resistance and diabetes, potentially affecting hepatic glucose and lipid metabolism and the function and survival of pancreatic islet cells.¹² To clarify these associations, a

systematic review is needed to consolidate current evidence on the relationship between vitamin D levels and prediabetes. This study aims to conduct a thorough review of the evidence linking vitamin D with the incidence of prediabetes.

METHODS

Protocol

The study was conducted with stringent adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, ensuring rigorous methodological standards. By following PRISMA 2020, the study emphasizes transparency, reproducibility, and methodological rigor throughout the review process. This commitment was evident in the systematic approach to literature search, data extraction, and synthesis of findings, all of which were designed to minimize bias and enhance the reliability of the conclusions.

Criteria for Eligibility

This study offers a comprehensive analysis of research

from the past decade on the impact of vitamin D in patients with prediabetes. By systematically reviewing and synthesizing data from a diverse range of studies, the research aims to identify trends and enhance patient care strategies for this at-risk population. The primary objective is to highlight key themes across the literature, thus deepening the understanding of vitamin D's role in prediabetes. To ensure methodological rigor, the study applied stringent inclusion and exclusion criteria: only peer-reviewed studies published in English between 2012 and 2024, with a DOI for verification, were considered. Non-research documents such as reviews, editorials, and duplicate entries were excluded to maintain the focus and integrity of the dataset. This meticulous approach guarantees that the data is both relevant and reliable, providing a solid foundation for drawing meaningful conclusions and advancing clinical practice.

Search Strategy

We used "vitamin D OR pre diabetes OR role" as keywords. The

search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Data retrieval

The authors conducted a thorough initial assessment of each article by reviewing abstracts and titles to determine relevance before proceeding with a detailed analysis. Only studies that met the study's objectives and adhered to predefined inclusion criteria were considered for further examination. This methodical approach facilitated the identification of clear and consistent patterns across the research. Full-text articles were limited to those published in English to maintain language consistency. A stringent screening process was employed to select content that was directly relevant to the study's focus and adhered to all inclusion criteria, systematically excluding studies that did not meet these standards. The evaluation encompassed a wide range

of factors, including study design, titles, authors, publication dates, research locations, and methodologies. This comprehensive approach ensured that the included studies were of the highest relevance and quality, thereby strengthening the reliability and robustness of the study's conclusions.

Quality Assessment and Data Synthesis

The authors performed a detailed review of each article's abstract and title to determine which warranted further investigation. Following this preliminary screening, all relevant documents underwent an in-depth analysis. The results from this evaluation informed the selection process, ensuring that only the most pertinent studies advanced to detailed examination. This rigorous approach streamlined the selection process, facilitating a comprehensive and nuanced assessment of existing research and its context.

Table 1. Search Strategy

<i>Database</i>	<i>Search Strategy</i>	<i>Hits</i>
Pubmed	<i>("vitamin D" AND "pre diabetes" AND "role")</i>	10
Science Direct	<i>("vitamin D" AND "pre diabetes" AND "role")</i>	305
Sagepub	<i>("vitamin D" AND "pre diabetes" AND "role")</i>	57

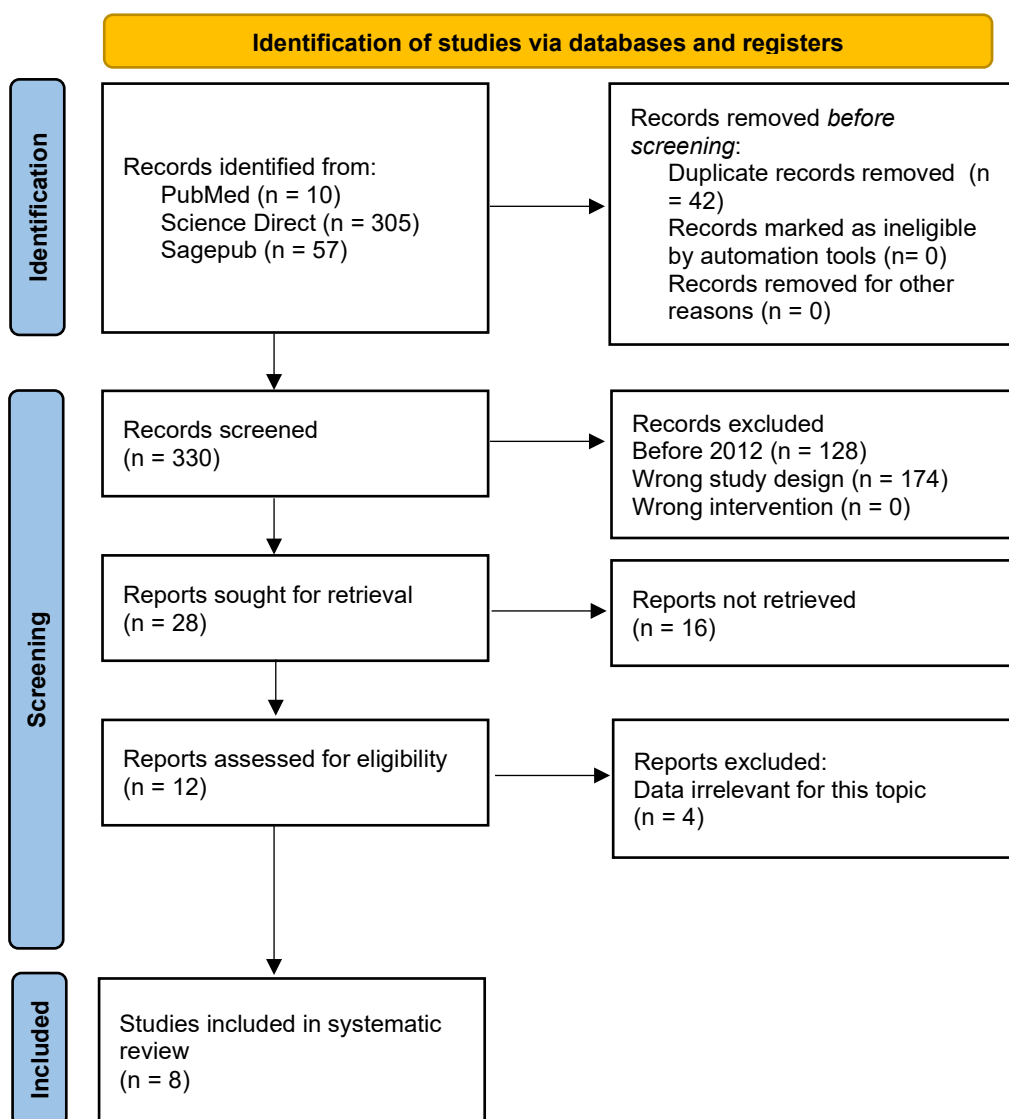


Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(Hosei ni et al., 2012)	(Ain et al., 2015)	(Yu et al., 2020)	(Zhan g et al., 2020)	(McC arthy et al., 2022)	(Khan et al., 2023)	(Pittas et al., 2023)	(Valer- Martin ez et al., 2024)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	Yes	Yes	No	No	No	No	No	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	No	No	No	No	No	No	No
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes.	No.	Yes.	Yes.	No.	Yes.	Yes.	No.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULT

We initiated the investigation by systematically gathering a significant assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected eight papers that were considered very pertinent to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our study, we have included a concise summary of the evaluated information in Table 3.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Hoseini et al. ¹³ (2012)	Iran	ECT	45 participants	The effect of vitamin D on insulin sensitivity in pre-diabetes patients was not significant, with no significant effect observed in group A. Oral vitamin D treatment had no effect on insulin sensitivity, suggesting a need for a randomized double-blind study to investigate its effect on insulin resistance.
Ain et al. ¹⁴ (2015)	Pakistan	Case Control	272 patients	Vitamin D levels showed an inverse correlation with fasting plasma glucose (FPG) and a significant association with pre-diabetes, suggesting that vitamin D may play a crucial role in the pathogenesis of pre-diabetes, compared to normoglycaemia.
Yu et al. ¹⁵ (2020)	China	Systematic Review	12 studies	The study showed no significant association between low serum levels of 25-hydroxy vitamin D and high risk of prediabetes. However, meta-analysis showed greater changes in 2-hour oral glucose tolerance test in individuals with

				prediabetes treated with vitamin D compared to those treated with placebo. The study also found no significant differences in changes of hemoglobin A1c, fasting plasma glucose, and homeostatic model assessment of insulin resistance.
Zhang et al.¹⁶ (2020)	China	Systematic Review	8 studies	Vitamin D supplementation significantly reduced the risk of Type 2 Diabetes Mellitus (T2DM) in nonobese subjects, but not in obese ones. The reversion of prediabetes to normoglycemia occurred in 21.2% of vitamin D supplemented participants, while the control group experienced a higher rate.
McCarthy et al.¹⁷ (2022)	Ireland	Prospective Cohort	9100 participants	Deficient vitamin D levels are linked to an increased likelihood of prevalent diabetes. Those with vitamin D levels below 30 nmol/L have a 62% higher likelihood of developing prediabetes compared to those with a higher level. The progression from prediabetes to diabetes is 32.5% between wave 1 and 3.
Khan et al.¹⁸ (2023)	UK	Systematic Review	13 studies	Thirteen randomized controlled trials identified incidences of Type 2 Diabetes, with seven showing no significant impact of vitamin D. However, 10 trials analyzed the impact of vitamin D supplementation

				on patients' HOMA-IR, with six showing a decrease and four increasing. Further research is needed to influence clinical guidelines on vitamin D supplementation.
Pittas et al.¹⁹ (2023)	USA	Systematic Review	3 studies	Vitamin D, a crucial vitamin, has been shown to reduce the risk of diabetes by 15% in randomized trials comparing cholecalciferol, cholecalciferol, and eldecalcitol. This reduction was not different in prespecified subgroups, and even among those with a serum 25-hydroxyvitamin D level of at least 125 nmol/L, vitamin D increased the likelihood of regression to normal glucose regulation by 30%. However, no evidence was found for adverse events.
Valer-Martinez et al.²⁰ (2024)	Spain	Prospective Cohort	-	The study found a significant inverse association between predicted levels of serum vitamin D and the risk of developing T2D in a total of 18,594 participants, with 209 diagnosed with T2D after 238,078 person years of follow-up. This association was based on sensitivity analyses and potential confounders.

DISCUSSION

Vitamin D supplementation has been implicated in mitigating the risk of developing Type 2 Diabetes Mellitus (T2DM) among individuals with prediabetes through two primary biological mechanisms.¹⁶ Firstly, vitamin D plays a crucial role in insulin synthesis and secretion by pancreatic beta cells, which house elements of the vitamin D endocrine system.²¹ Vitamin D deficiency is associated with diminished insulin secretion; conversely, supplementation restores insulin production and enhances islet cell secretory functions. This is achieved through the modulation of the local renin-angiotensin system, which plays a role in islet beta-cell function.^{22,23} Secondly, vitamin D improves insulin sensitivity in peripheral tissues—such as adipose tissue, muscle, and hepatocytes—through its receptor-mediated effects. This includes the enhancement of insulin receptor expression and regulation of calcium metabolism, which collectively contribute to improved insulin sensitivity.²⁴

Despite these proposed mechanisms, the effectiveness of vitamin D in diabetes prevention remains a subject of debate. A 2014 meta-analysis concluded that vitamin D3 supplementation did not significantly reduce diabetes risk in prediabetic populations.²⁵ This finding was corroborated by a 2018 review, although the review did suggest a potential reduction in T2DM incidence in specific subgroups with prediabetes.²⁶ The current study contributes to this ongoing discussion by incorporating data from three large, long-term trials, which collectively encompass 78.5% of the participant pool, thus enhancing the statistical power of the analysis. Nevertheless, the two largest trials—D2d and DDVP—produced nonsignificant results, with D2d specifically powered to detect a 25% risk reduction, but observing a less pronounced effect.^{19,27}

Another critical aspect to consider is the differential effectiveness of vitamin D supplementation in obese individuals. Due to vitamin D's fat-soluble nature, it tends to be sequestered in adipose

tissue, requiring higher doses to achieve adequate serum levels. Furthermore, obesity affects vitamin D metabolism by decreasing hepatic 25-hydroxylase activity, leading to reduced serum 25(OH)D concentrations.^{28,29} The reliability of subgroup analyses based on mean baseline BMI is compromised without detailed individual patient data, as variability within trial populations can skew outcomes. This limitation was notably evident in the D2d study.¹⁶

The American Diabetes Association (ADA) advises lifestyle interventions and magnesium supplementation for diabetes prevention, but it does not support routine vitamin D or multivitamin use for glycemic control due to insufficient evidence.³⁰ While intensive lifestyle interventions have demonstrated significant efficacy in reducing diabetes risk, vitamin D supplementation may offer supplementary benefits for individuals unable to adhere to rigorous lifestyle changes. Future research is necessary to evaluate whether adjunctive vitamin D

therapy, in combination with lifestyle interventions, can further decrease the incidence of T2DM.^{29,31}

CONCLUSION

Research has suggested that vitamin D supplementation may reduce the risk of developing Type 2 Diabetes Mellitus (T2DM) in individuals with prediabetes by improving insulin synthesis and secretion by pancreatic beta cells and enhancing insulin sensitivity in peripheral tissues through receptor-mediated effects and calcium regulation. However, the effectiveness of vitamin D in diabetes prevention is a topic of debate. While a 2014 meta-analysis and a 2018 review did not find significant overall benefits, some subgroup analyses indicated potential risk reductions. Recent large, long-term trials, such as the D2d trial, have not consistently supported these findings, showing nonsignificant results. Furthermore, the effectiveness of vitamin D supplementation may be limited in obese individuals due to its fat-soluble nature and altered metabolism. Despite the potential

benefits, the American Diabetes Association does not recommend routine vitamin D supplementation for glycemic control and emphasizes the need for further research to assess the potential benefits of combining vitamin D with lifestyle modifications.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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