VITAMIN D DEFICIENCY AS A RISK FACTOR OF INSULIN RESISTANCE AND TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW

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Abstract

Objectives: To study the recently published literature on the relationship between vitamin D deficiency and insulin resistance (IR) and type-2 diabetes (T2D). **Methods:** We conducted a thorough search of PubMed, SCOPUS, Web of Science, and Google Scholar to find pertinent literature. Rayyan QRCI was utilized during the entire process. **Results:** We included ten studies with a total of 30113 patients and 12439 (41.3%) were males. The follow-up duration ranged from 0.5 year and 13.5 years. The reported vitamin D level ranged from 6.3 ng/mL to 47.9 ng/mL. This study included a variety of populations including the general population, T2D patients, and prediabetes patients. Higher levels of vitamin D may be protective against the development of diabetes. The included studies demonstrated that vitamin D deficiency is significantly associated with hyperinsulinemia, prediabetes, IR, and T2D. **Conclusion:** The results of this systematic analysis showed that the risk of T2D, prediabetes, and IR is markedly increased in individuals with a vitamin D deficit. More study is required, especially in those with poor glucose tolerance and/or fasting glucose, who may not be obese but are at a high risk of developing diabetes. It is necessary to do longer-term research in order to verify these results and investigate any possible pathophysiological bases.

Keywords: Vitamin D; Deficiency; Type 2 diabetes; Insulin Resistance; Systematic review.

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Introduction

The prevalence of T2D is high throughout the world, and the condition has a crippling financial cost. Ninety percent of the 4.7 million people in the UK with a diabetes diagnosis are thought to have T2D. This number has more than doubled in the last 20 years, and by 2030, it is expected to surpass 5.5 million [1]. The treatment of T2D and its consequences cost the NHS (National Health Service, UK) £8.8 billion in 2010; it is predicted that these expenses will almost quadruple by 2035 [2]. Furthermore, despite the availability of effective pharmaceutical treatments, the illness and its complications place a heavy burden on people who are afflicted. In an effort to further manage blood glucose levels and so lower the chance of acquiring T2D, numerous research have evaluated preventative methods against the disease [3]. As a result, new, affordable medications have been proposed.

Vitamin D is one such treatment that has been well-studied. Vitamin D, well-known for its function in calcium metabolism, is first transformed to 25(OH)D in the liver and then to 1,25(OH)2D in the kidneys. This active metabolite is in charge of intestinal calcium absorption and bone mineralization. Thus, it is widely known that a severe vitamin shortage leads to impaired bone formation, which is characterized by rickets in children and osteomalacia in adults. Nonetheless, vitamin D's contribution to enhancing insulin sensitivity and pancreatic beta cell activity is not as well known. Its method of action is similar to that of the anti-diabetic medication pioglitazones; it primarily involves promoting the expression of insulin receptors and facilitating peroxisome proliferator-activated response-δ [4], which enhances glucose absorption in peripheral tissues. Additionally, it increases the secretion of insulin by activating the vitamin D receptor in the pancreatic beta cell [5].

As a result, vitamin D has been shown to lower patients' HbA1c levels, fasting glucose, and risk of developing T2D [6, 7]. The opposite is also true in the same way. Due to lowered insulin secretion and glucose absorption, their absence may raise the chance of developing T2D. This was supported by a meta-analysis that indicated people with vitamin D deficiency had a 54% chance of having pre-diabetes [7]. This is corroborated by a cross-sectional study conducted on Indian women, which discovered that many T2D patients had vitamin D deficiency [8]. We conducted a systematic review of the relationship between vitamin D deficiency and IR and T2D.

Methodology

Study Design and Duration

The methods used in this systematic review were compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance [9]. The comprehensive evaluation began in May 2019.

Search strategy

A thorough search was carried out utilizing four important databases: PubMed, SCOPUS, Web of Science, and Google Scholar to locate pertinent content. We looked through databases with just English-language content, taking into consideration each one's particular requirements. We transformed the following keywords into PubMed Mesh terms in order to locate the pertinent papers; "Vitamin D deficiency," "Insulin resistance," "Type 2 diabetes," and "Risk." "OR," "AND," and "NOT," three Boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection criteria

Inclusion criteria:

We considered the following criteria for inclusion in this review:

- Studies that discussed the relationship between vitamin D deficiency and IR and T2D.
- Adult participants (>18 years).
- Studies conducted between (2010-2021).
- Only human subjects.
- English language.
- Free accessible articles.

Exclusion criteria:

- The following study designs were excluded: case reports, comments, replies, and letters to the editors.
- Genetic studies.

Data extraction

Rayyan (QCRI) was used for two output verifications of the search strategy [10]. The researchers assessed the abstracts' and titles' relevance to the combined search results using inclusion/exclusion criteria. Every manuscript that satisfied the inclusion requirements was given thorough consideration by the reviewers. The writers discussed dispute-resolution techniques. Utilizing a pre-made data extraction form, the authorized study was uploaded. The authors extracted data on the study title, authors, study year, country, participants, age, gender, follow-up

duration, type of patients, vitamin D level, and main outcomes.

Strategy for data synthesis

A qualitative evaluation of the research's findings and components was produced by compiling summary tables with data from pertinent studies. Once the data for the systematic review was collected, the optimal method for utilizing the data from the included study articles was selected.

Search results

The systematic search produced 1428 study articles, of which 790 duplicates were eliminated. After 638 studies had their titles and abstracts screened, 578 were not included. After 60 reports were requested to be retrieved, 3 articles were found. After screening 57 studies for full-text assessment, 24 were rejected due to incorrect study results, 19 were rejected due to incorrect population type, 2 articles were editor's letters, and 2 were abstracts. This systematic review included ten eligible study articles. A synopsis of the procedure for choosing studies is provided in **Figure 1.**

Results

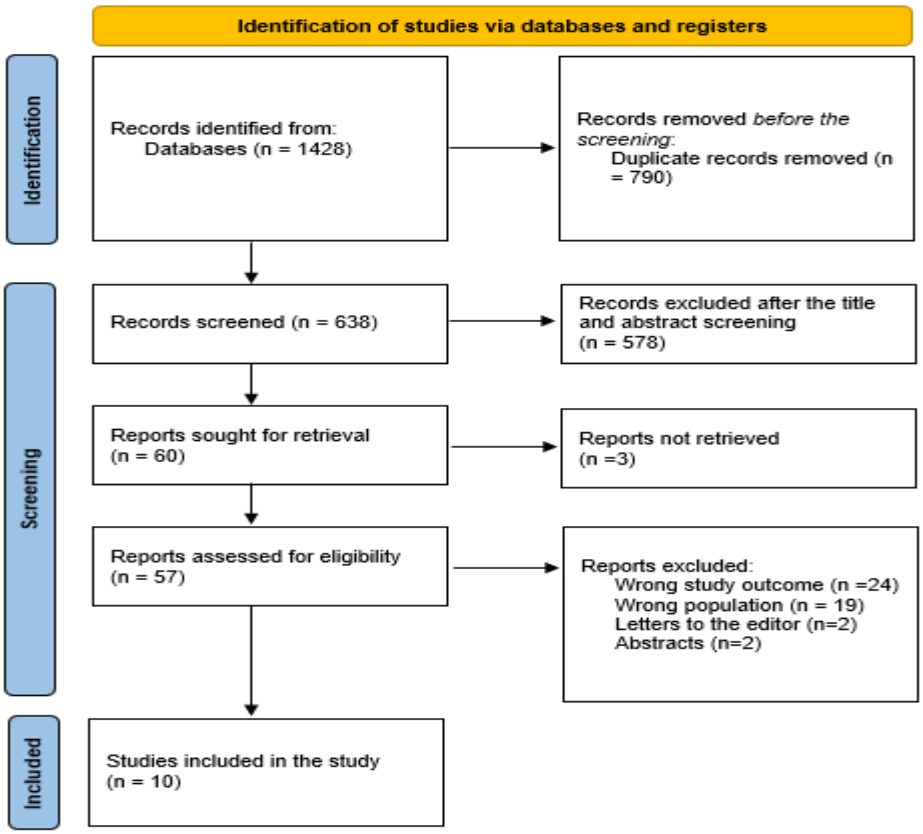

Figure (1): Study selection is summed up in a PRISMA flowchart.

Characteristics of the included studies

Table (1) shows the sociodemographic details of the research articles that are included. Our results included ten studies with a total of 30113 patients and 12439 (41.3%) were males. Four studies were case-controls [13, 15, 16, 17], three were cross-sectional [11, 14, 19], and three were prospective cohorts [12, 18, 20]. Two studies were conducted in India [13, 14], two in the USA [15, 18], one in Peru [11], one in Ireland [12], one in Greece [16], one in Nigeria [17], one in Iran [19], one in Spain [20].

Table (2) presents the clinical characteristics. The follow-up duration ranged from 0.5 year [17] and 13.5 years [20]. The reported vitamin D level ranged from 6.3 [15] ng/mL to 47.9 ng/mL [17]. This study included a variety of populations including the general population [12, 18, 19, 20], T2D patients [11, 13, 17], and prediabetes patients [14, 15]. This variety may be a source of bias and we did not conduct a subgroup analysis. Higher levels of vitamin D may be protective against the development of diabetes [18]. The included studies demonstrated that vitamin D deficiency is significantly associated with hyperinsulinemia

[11], prediabetes [12, 14], IR [13, 16, 17, 19], and T2D [13, 15, 20].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Age	Gender (Males)
Urrunaga-Pastor et al., 2019 [11]	Cross-sectional	Peru	Normal (n=144) & Deficiency (n=60)	38.5 ± 10.6	40 (19.6%)
Dutta et al., 2014 [12]	Prospective cohort	Ireland	Normoglycaemia (n = 4612), Prediabetes (n = 242), & Diabetes (n = 418)	62.1-67.7	2448 (46.4%)
Dhas et al., 2019 [13]	Case-control	India	Control (n = 90) & T2D (n = 90)	30-50	102 (56.7%)
Mishra et al., 2020 [14]	Cross-sectional	India	60	28-62	44 (77.3%)
Wang et al., 2020 [15]	Case-control	USA	Pre-diabetic subjects (n=30) & Normoglycemic controls (n=30)	45	10 (16.7%)
Archontogeorgis et al., 2019 [16]	Case-control	Greece	92	51.5 ± 11.9	81 (88%)
17.Herman et al., 2012 [17]	Case-control	Nigeria	Cases (n = 120) & Controls (n = 60)	55.2 ± 6.9	51 (28.3%)
Zhong et al., 2018 [18]	Prospective cohort	USA	3311	53.3 ± 12.5	1215 (36.7%)
Ehrampoush et al., 2021 [19]	Cross-sectional	Iran	2160	39.8 ± 10.8	1103 (51.1%)
Wimalawansa et al., 2018 [20]	Systematic review	USA	18,594	38 ± 12.2	7345 (39.5%)

*NM=Not-mentioned

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Population type	Follow-up duration (years)	Vitamin D level (ng/mL)	Main outcomes
Urrunaga-Pastor et al., 2019 [11]	Patients without T2D	NM	19 - 33.3	In euthyroid individuals without T2D, there is a correlation between vitamin D deficiency and hyperinsulinemia following oral glucose tolerance test (OGTT).
Dutta et al., 2014 [12]	Prediabetes population	4	18.96 - 23.48	Baseline vitamin-D and 2h blood glucose independently predicted progression to diabetes.
Dhas et al., 2019 [13]	Middle-aged T2D patients	NM	9.93 - 30.91	The optimum 25(OH)D concentration may stop IR from starting and T2D from progressing after that.
Mishra et al., 2020 [14]	Patients with prediabetes	2.5	10 - 33.5	Prediabetes and low vitamin D levels are related. In those with prediabetes, vitamin D deficiency or insufficiency has been linked to worsening IR.
Wang et al., 2020 [15]	Patients with prediabetes	NM	6.3 - 7.82	An increased serum 25OHD content is linked to a decreased incidence of T2D.
Archontogeorgis et al., 2019 [16]	Patients with OSA	4	7.8 - 38.9	Patients with IR who had OSAS were substantially more likely to be deficient in vitamin D. In this sample, there was a correlation between the likelihood of IR and low 25(OH)D levels.
17.Herman et al., 2012 [17]	Patients with T2D	0.5	24.19 - 47.9	When comparing T2D patients to healthy controls, hypovitaminosis D is considerably more prevalent in the former group. Among those with T2D, there was a noteworthy inverse relationship between vitamin D and IR.
Zhong et al., 2018 [18]	Patients with Disbetes	7.7	NM	In USD, higher levels of 25(OH)D may be protective against the development of diabetes, especially in those with detectable levels of 25(OH)D2 and 25(OH)D3.
Ehrampoush et al., 2021 [19]	General population	NM	13.9 - 32.2	The 2-hour postprandial insulin, 2-hour postprandial blood glucose, 2-hour postprandial insulin, HOMA2-IR as a glycemic index, and IR all demonstrated an inversely significant association with the vitamin D level.
Wimalawansa et al., 2018 [20]	General population	13.5	7.1 - 32.7	The results imply that a lower risk of acquiring T2D may be linked to baseline levels of vitamin D that are greater.

Discussion

This systematic review included longitudinal observational and case-control studies and demonstrated that vitamin D deficiency is significantly associated with hyperinsulinemia [11], prediabetes [12, 14], IR [13, 16, 17, 19], and T2D [13, 15, 20]. Higher levels of vitamin D may be protective against the development of diabetes [18]. A systematic review by **Mitri *et al.*** reported that lower vitamin D status and intake are linked to a higher risk of incident T2D in observational studies, suggesting a biologically plausible role for vitamin D in T2D. However, in small underpowered trials or post hoc analyses of larger trials, the impact of vitamin D supplementation on glycemic outcomes was not evident. Overall, the evidence currently available does not support the claim that increasing 25(OH)D concentration can ameliorate T2D. Large trials conducted in well-defined populations (e.g., prediabetes, early T2D, and Whites versus non-Whites) specifically designed to test the hypothesis that vitamin D status is a direct contributor to T2D pathogenesis are required to confirm a potential beneficial effect of vitamin D on T2D [21].

Another systematic review found insufficient data to support the idea that vitamin D administration considerably postpones the onset of T2D. Nonetheless, in a few trials, vitamin D supplementation was seen to affect individuals' levels of IR. Randomized controlled trials will probably be necessary to see whether this can stop the onset of T2D.

While there is strong evidence linking vitamin D levels to the possibility of acquiring T2D, other studies come to a different conclusion. Following an average of 7.3 years of observation, approximately 6.3% of postmenopausal women with varied racial origins who had vitamin D insufficiency and got vitamin D subsequently acquired T2D. After accounting for a number of risk factors, there was no correlation found in this study between the incidence of T2D and vitamin D levels [23]. Another study by Qi et al. found no statistically significant difference in vitamin D concentrations between those who acquired T2D and those who did not. Of the 596 participants, 138 of them developed T2D. The results held up even after controlling for confounders [24].

two meta-analyses assessed vitamin D's impact. Haroon and associates examined a number of research that addressed how vitamin D affected glycemic measurements in people with T2D. Although vitamin D was found to have a positive effect on glycemic control in short-term studies, which were defined as follow-ups of three months or less, the studies' validity made the data insufficient. Long-term studies—defined as a follow-up of more than three months—contradicted this conclusion further by finding no appreciable change in either HOMA-IR or HbA1c [25]. Finally, taking into account the variation of vitamin D levels in these people, **Lips *et al.*** analyzed the majority of vitamin D research conducted before 2016—cohorts, RCTs, and meta-analyses on healthy participants, prediabetes, and T2D [26]. Numerous research were considered, thus this covered a range of backgrounds, including gender, race, and obesity. It discovered erratic outcomes. A small number of studies showed clinical benefit, whereas the majority showed no improvement above placebo. If any significant effects did occur, they were frequently negligible, casting doubt on vitamin D's therapeutic applicability in these investigations [27]. For instance, vitamin D did not affect FPG, HbA1c, or IR in more than 15 RCTs; but, in four trials involving participants who had prediabetes, FPG dropped by 0.32 mmol/L.

Limitations

The research data varied amongst the trials in a number of ways, including sample size, participant ethnicity, patient categories, and baseline vitamin D levels. Furthermore, the majority of trials did not account for variables that affect vitamin D levels, such as exposure to sunlight, degree of physical activity, and renal function. Similarly, the majority of clinical trials did not take into account variables that affect IR, such as nutrition, degree of physical activity, and family history.

Conclusion

The results of this systematic analysis showed that the risk of T2D, prediabetes, and IR is markedly increased in individuals with a vitamin D deficit. More study is required, especially in those with poor glucose tolerance and/or fasting glucose, who may not be obese but are at a high risk of developing diabetes. It is necessary to do longer-term research in order to verify these results and investigate any possible pathophysiological bases.

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