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## Vitamin D Supplementation and Glycaemic Control in Type 2 Diabetes: A Narrative Review of Randomised Trials

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### ABSTRACT

Low circulating vitamin D is common in people with type 2 diabetes, and it has long been suspected that correcting it might improve blood glucose. Observational studies, laboratory work on the pancreatic beta cell and a handful of small trials have kept the idea alive. This narrative review asks what randomised trials published up to the end of 2013 can actually say about vitamin D supplementation and glycaemic control in type 2 diabetes. It draws on the biology of vitamin D, on epidemiological associations, on reported supplementation trials and on the methodological literature that governs how such trials should be read, and it reports no new data. The trials point in different directions. Benefit, where it has been reported, tends to appear for insulin resistance rather than for glycated haemoglobin, in people who were deficient or glucose intolerant at the start, and in studies that were small and short. Trials in people with established diabetes and adequate vitamin D status have generally been unrewarding. Differences in dose, preparation, baseline status, duration and outcome measurement make the studies difficult to pool, and an association seen in cohorts is not evidence that supplementation changes glycaemia. The review concludes that supplementation is reasonable where deficiency is documented but is not established as a glucose-lowering treatment, and it sets out what a decisive trial would need to contain.

**Keywords:** Vitamin D; Type 2 diabetes; Glycaemic control; Insulin resistance; Randomised trials; Cholecalciferol; Narrative review

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**Article Class:** Review Article

### 1. Introduction

Few nutrients have attracted as much attention in recent years as vitamin D. Once regarded mainly as a vitamin for bone, it is now discussed in connection

with immunity, cancer, cardiovascular disease and metabolism (1, 2, 3). Low blood levels of its main circulating form, 25-hydroxyvitamin D, are reported in many countries, including sunny ones, and



the problem is often described as worldwide (4, 5). Type 2 diabetes is another condition that is growing in almost every region, so it is not surprising that people have asked whether the two are connected.

The question is a practical one. If supplementation lowered blood glucose even slightly, it would be cheap, widely available and easy to add to usual care. If it did not, then time, money and attention would be spent on something that cannot deliver. Enthusiasm has run ahead of evidence on more than one occasion in nutrition, and a candid look at what randomised trials have actually shown is overdue. We should say at the outset that this article reports no data of our own, and that it does not describe any local population or clinic.

This is a narrative review of published work up to the end of 2013. It first sets out why a link is biologically plausible, then looks at the epidemiology, then at the trials of supplementation in people with or at risk of diabetes, and finally at the problems of design and measurement that make those trials hard to compare. The thread running through it is a simple one: the strength of an idea is not the same as the strength of the evidence for it. The aim is to separate what has been shown from what has merely been repeated.

## 2. Literature Review

### 2.1 Vitamin D Status and How It Is Measured

Vitamin D is made in the skin on exposure to ultraviolet light and is also obtained from a small number of foods and from supplements. It is converted in the liver to 25-hydroxyvitamin D, the compound measured in clinical practice, and then in the kidney and other tissues to the active hormone (1). The blood level of the circulating form depends on sun exposure,

skin pigmentation, clothing, latitude, season and body fat, among other things, and seasonal swings are visible even in populations that are not obviously deficient (6).

Where to draw the line between sufficiency and deficiency is contested. An Endocrine Society guideline recommended a relatively high target for people at risk (7), while the Institute of Medicine concluded that a lower level meets the needs of most of the population (8), a position its authors later explained for clinicians (9). The disagreement matters for diabetes research, because a person classed as deficient in one trial may be classed as replete in another.

Measurement adds a further layer of uncertainty. Laboratories use different methods, and a comparison of assays showed that the same sample can yield noticeably different values depending on the method (10). Studies that rely on a single measurement, taken at a single time of year, therefore carry a source of noise that is rarely discussed in their abstracts.

### 2.2 Why a Link With Glucose Metabolism Is Plausible

The biological case rests on several observations. Pancreatic beta cells carry the vitamin D receptor and the enzymes that activate the vitamin, and the hormone has effects on calcium handling that are needed for insulin release (11, 12). Rats deprived of vitamin D secreted less insulin in response to glucose, and the defect was at least partly corrected when the vitamin was restored (13, 14). Mice lacking a functional vitamin D receptor showed impaired insulin secretory capacity (15). A response element for the vitamin has also been described in the promoter of the human insulin receptor gene, which would offer a route by which the hormone could influence insulin sensitivity in target tissues (16).



Inflammation provides a second route. Low-grade inflammation accompanies insulin resistance, and vitamin D modulates immune and inflammatory signalling, so a benefit through that pathway has been proposed (17, 18). Reviews of the field have also stressed that the vitamin may act on insulin resistance and on insulin secretion by separate mechanisms (19). These pathways are summarised in Figure 1.

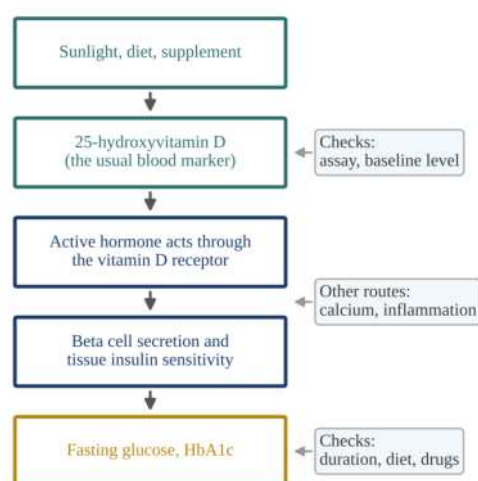


**Figure 1.** Proposed routes from vitamin D to glucose control, with the checks that surround them (schematic, not data).

Plausible biology is a reasonable reason to run a trial. It is not a reason to expect that trial to be positive. Much of the laboratory work was done in animals that were severely deprived of the vitamin, a state that bears little resemblance to the mild insufficiency seen in most people, and the doses and timescales involved differ greatly from human practice.

### 2.3 Observational Evidence

Several lines of observational work suggest that people with lower vitamin D status are more likely to have impaired glucose handling. In a national survey in the United States, lower levels were associated with a higher likelihood of diabetes, although the pattern varied by ethnic group (20). Low levels have also

been linked with the metabolic syndrome (21), with insulin resistance and impaired beta cell function (22), and with the same abnormalities among people at risk of diabetes (23). In a cohort of women, higher combined intake of vitamin D and calcium went with a lower risk of developing type 2 diabetes (24). Table 1 collects these lines of evidence and the main weakness of each.

The difficulty with all of these findings is the usual one. People with obesity, low physical activity, little outdoor exposure or chronic illness tend to have lower vitamin D levels and a higher risk of diabetes for reasons that have nothing to do with supplementation. Body fat in particular sequesters the vitamin and lowers its circulating level, so a low value may be a consequence of the metabolic state rather than a cause. Adjustment for such factors is always incomplete. The systematic reviews that have weighed this literature have said as much, noting that the observational data are consistent but cannot settle the matter (25, 27).

**Table 1.** Lines of evidence linking vitamin D to glucose metabolism.

| Line of evidence           | What it suggests                                            | Main weakness                               |
|----------------------------|-------------------------------------------------------------|---------------------------------------------|
| Laboratory and animal work | Deficiency impairs insulin secretion (13, 14, 15)           | Species and dose differ from human practice |
| Cohort studies             | Lower vitamin D status goes with more diabetes (20, 21, 24) | Confounding; reverse causation              |
| Cross-sectional studies    | Low status goes with insulin resistance (22, 23)            | Cannot show direction                       |
| Supplementation trials     | Mixed results (25, 26)                                      | Small, short, varied                        |

Note: Qualitative summary of the cited literature; no effect sizes are given because the sources differ in design and population.



## 2.4 Pharmacology of Supplementation

Trials do not all give the same thing. Cholecalciferol, the form made in skin, raises the circulating level more effectively than ergocalciferol (28), and the rise achieved depends on the dose, the duration and the starting level (29). Some trials use a large single dose, some use daily or weekly doses, and some deliver the vitamin in fortified food. Calcium is often given with it, which makes it hard to say which component, if either, is responsible for any change. Small differences of this kind matter little in a single trial but accumulate across a literature.

## 3. Materials and Methods

### 3.1 Scope and Question

The review asks one question in two parts. Does vitamin D supplementation improve glycaemic control in people with type 2 diabetes, and, if the answer depends on who is studied, on what does it depend? Glycaemic control is taken to mean fasting glucose and glycated haemoglobin (HbA1c), together with indices of insulin resistance and insulin secretion where these were the main outcomes. The review is confined to humans and to work published in English up to the end of 2013.

### 3.2 Literature Assembly

The sources are peer-reviewed publications in four areas: the biology and measurement of vitamin D, observational studies of vitamin D status and glucose handling, randomised trials and meta-analyses of supplementation, and the methodology of trials and reviews. Landmark papers, systematic reviews and trials that were cited repeatedly by others were given priority, which is the usual approach to narrative synthesis (30).

We did not run a formal systematic search and do not claim one. This is a narrative synthesis, and the choice of sources

reflects our judgement. Reviews that follow the reporting standard for systematic reviews (31) describe a search strategy, databases and exclusion rules, and ours does not. A reader should treat the list of trials as representative rather than complete, and should not expect the conclusions to be those of a meta-analysis.

### 3.3 Appraisal Framework

To judge how far a report can be trusted, we asked four questions of every trial. Who was enrolled, and what was their vitamin D status and glycaemic state at the start? What was given, in what dose and for how long, and was the circulating level measured afterwards? How was glycaemic control measured, and was the follow-up long enough for that measure to respond? And was the trial reported in enough detail, in line with accepted reporting guidance for randomised trials (32), to allow the result to be reused? Table 2 lists the trials discussed in the next section with their populations.

**Table 2.** Selected supplementation trials and the direction of what was reported.

| Study               | Population                                     | Reported direction                       |
|---------------------|------------------------------------------------|------------------------------------------|
| Pittas 2007 (33)    | Older adults without diabetes; calcium with D3 | Benefit only in impaired fasting glucose |
| Nagpal 2009 (34)    | Centrally obese men                            | Better insulin sensitivity               |
| von Hurst 2010 (35) | Deficient, insulin-resistant women             | Lower insulin resistance                 |
| Jorde 2009 (36)     | Diabetes, normal vitamin D status              | No gain in control                       |
| Witham 2010 (37)    | Type 2 diabetes; several doses                 | No convincing change                     |
| Talaie 2013 (38)    | Type 2 diabetes; single large dose             | Improved insulin resistance              |
| Nikooyeh 2011 (39)  | Type 2 diabetes; fortified drink               | Better glycaemic control                 |

Note: Population and design are as described by the original authors; the last column gives direction only and no magnitudes.



## 4. Results

### 4.1 Trials in People Without Established Diabetes

The most encouraging reports come from people who did not yet have diabetes. In a trial of older adults without diabetes, supplementation with calcium and vitamin D was followed by a smaller rise in insulin resistance among those who had impaired fasting glucose at baseline, while those with normal glucose showed no such effect (33). The finding is interesting because it is conditional: it suggests that benefit, if any, appears where glucose handling is already beginning to fail.

Two further trials reported improved insulin sensitivity after supplementation. One enrolled centrally obese men and used a short course (34). The other enrolled South Asian women living in New Zealand who were both insulin resistant and vitamin D deficient, and reported a lower insulin resistance in the supplemented group (35). Both trials were modest in size, both had short follow-up, and neither enrolled people who had type 2 diabetes. They tell us something about insulin resistance in deficient people and little about treatment of diabetes. Read this way, the absence of an effect in a small trial is not evidence that no effect exists.

### 4.2 Trials in Type 2 Diabetes

Results in people with diagnosed diabetes are less consistent. A trial of cholecalciferol in patients whose vitamin D levels were already normal found no improvement in glycaemic control (36). That is what one would expect if benefit depends on correcting a deficit. A trial that compared several doses in patients with diabetes, designed around markers of vascular health, did not find a convincing change in those markers (37). The point is not that a trial is poor, only that its result travels less far than its abstract suggests.

Other reports are more favourable. A single large dose of the vitamin was followed by an improvement in indices of insulin resistance in patients with type 2 diabetes (38), and a fortified yogurt drink, with or without added calcium, was followed by better glycaemic control in a randomised trial in diabetic patients (39). In each case the setting, the product and the baseline status differed from those of the trials just described, which is part of the difficulty. A reader of a trial report wants to know, above all, whether the result would carry over to people unlike those enrolled.

The systematic reviews give the same mixed picture. Early reviews found that the supplementation trials were few, small and inconsistent, and that any effect on glucose was uncertain (25, 27). A later meta-analysis found no clear overall effect on glycaemic control or insulin resistance, with a suggestion that benefit might be confined to people who were glucose intolerant or insulin resistant at baseline (26). The reported benefit has tended to appear for insulin resistance, a research measure, rather than for HbA1c, the measure on which clinical care is judged (40). This helps explain why trials of the same vitamin can point in opposite directions.

### 4.3 Why the Trials Disagree

Several features of the trials, listed in Table 3, would be enough on their own to produce disagreement. Baseline status heads the list. A person who is already replete has little room to improve, and the trial that enrolled such people found nothing (36), whereas deficient participants were the ones in whom benefit was reported (35). Many trials did not select participants by measured status at all, so that a modest average benefit in the deficient is diluted by a null result in the rest. Checking the baseline level before



reading the result is a simple step. It is a habit worth keeping even when the expected answer seems obvious.

Dose and preparation also differ, as noted above, and so does the level actually reached, which many reports do not give (28, 29). When the circulating level is not reported, a null result cannot be separated from a failure to raise the level. The pooling of unlike studies adds further difficulty. Statistical measures of inconsistency across trials exist for this purpose (41), and where they are high a single summary figure is of doubtful meaning.

**Table 3.** Sources of disagreement between trials and what would reduce them.

| Source                    | Effect on the result                             | Remedy                                  |
|---------------------------|--------------------------------------------------|-----------------------------------------|
| Baseline vitamin D status | Replete participants have little to gain (7, 36) | Enrol by measured status                |
| Dose and preparation      | Raised levels differ (28, 29)                    | Report preparation, dose, level reached |
| Assay variation           | Same sample, different value (10)                | Standardised assay                      |
| Short follow-up           | HbA1c lags behind (42)                           | Follow beyond one HbA1c cycle           |
| Small samples             | Unstable, exaggerated effects (43)               | Adequate numbers; report intervals      |
| Pooling unlike studies    | Heterogeneity (41)                               | Examine subgroups, not only totals      |

Note: Drawn from the methodological and clinical literature cited in the text; not attributed to any single trial.

Timing is another source of disagreement and is shown in Figure 2. HbA1c reflects glucose over roughly the preceding two to three months, and laboratory guidance on its use stresses this point (42). A trial that is too short therefore cannot show a change in HbA1c even if insulin action has improved, and the outcome that responds fastest may not be the outcome that matters

most. A system that has had time to adjust behaves differently from one measured too early.



Schematic; spacing is not to scale

**Figure 2.** Timeline of what a supplementation trial can and cannot see (schematic; spacing is not to scale and is not data).

#### 4.4 Where Benefit Is Most Plausible

If the findings are set side by side, a pattern emerges. Benefit is judged most plausible in people who are deficient at baseline and who have impaired glucose handling that has not yet progressed to established diabetes, and least plausible in those who are replete (Figure 3). This is a reading of the literature rather than a result, and it comes from small studies. Even so, it fits the biology and the pooled findings, and it suggests a hypothesis that a properly designed trial could test. That is a modest conclusion, and it is the one the evidence currently allows.

Rows: baseline vitamin D status

|              | Glucose intolerant | Early type 2 diabetes | Established type 2 diabetes |
|--------------|--------------------|-----------------------|-----------------------------|
| Deficient    | more plausible     | more plausible        | uncertain                   |
| Insufficient | uncertain          | uncertain             | least plausible             |
| Replete      | least plausible    | least plausible       | least plausible             |

Qualitative judgement, not data

**Figure 3.** Where benefit is judged more or less plausible, by baseline vitamin D status and glycaemic state (qualitative matrix, not data).

A reasonable scepticism is also in order. The field has the features that lead to unreliable findings: small studies, flexible



outcomes and a topic of wide public interest (43).

## 5. Discussion

### 5.1 Interpretation

The central finding of this review is a conditional one. Vitamin D supplementation has not been shown to lower glucose in people with established type 2 diabetes who are vitamin D replete, and it has not been shown to be harmful, a point on which a meta-analysis of randomised trials, though it examined mortality rather than glucose, was reassuring (44). There are hints of a benefit for insulin resistance in people who are deficient or glucose intolerant, but these come from small, short studies and have not been shown to translate into better HbA1c or fewer complications (26, 45).

The practical reading is cautious. Where deficiency has been documented, correcting it is reasonable on general grounds, since the vitamin has well-established roles in the skeleton (3), and any glycaemic gain would be a bonus rather than the reason. Where a person is replete, there is no good evidence that taking more would improve glucose control. Nothing in this reading argues against correcting deficiency; it argues for measuring what happens afterwards.

Population matters as well. Low vitamin D status has been reported across Europe and Asia (5), but its prevalence and causes differ between regions and age groups. Several of the trials that reported benefit enrolled groups known to be at risk of deficiency (35, 39), so their results may not transfer to people with ample sun exposure, and a trial in a replete population says little about deficient people. Any statement about benefit has to carry its population with it.

The distinction between treating a deficiency and treating diabetes deserves

emphasis. Popular accounts often blur the two. A deficiency is corrected by replacing what is missing, whereas a glucose-lowering drug is expected to work in people whose vitamin status is adequate. The trials discussed here suggest that vitamin D behaves like the former.

### 5.2 Limitations

This review shares the limitations of the narrative form. The selection of sources reflects judgement, no formal search was run, and we did not appraise each study using a scored instrument. Trials that did not find an effect may be under-represented because they are less often cited, and there is no way to rule out the omission of relevant work. Reviews of this kind are more useful when they say where the evidence stops than when they smooth over the gap.

The evidence itself also limits what can be said. The trials differ in population, product, dose, duration and outcome, and a conclusion that holds for one will not necessarily hold for another. Most are small, and the review stops at the end of 2013, so later and larger trials may change the picture.

### 5.3 Future Work

Three needs stand out. The first is a trial that enrolls participants by measured baseline status, with enough deficient and replete people to test the hypothesis in Figure 3 directly, and with the circulating level measured with a standardised assay at the start and the end (10). The second is follow-up long enough for HbA1c to respond, and ideally long enough to say something about the need for medication. The third is a pre-specified analysis of insulin resistance and beta cell function alongside HbA1c, so that the pattern that has appeared in small trials can be confirmed or abandoned. These points apply with equal force to any nutrient



studied as a treatment, not only to vitamin D.

## 6. Conclusion

The case for vitamin D as a treatment for type 2 diabetes rests on plausible biology and on consistent observational associations, but the randomised trials have not delivered a clear answer. Benefit, where reported, has been seen for insulin resistance in people who were deficient or glucose intolerant, and trials in diabetic patients with adequate status have been unrewarding. Differences in design make the studies hard to combine.

For now, vitamin D should be regarded as a nutrient to be supplied where deficiency exists, not as a glucose-lowering treatment. A large, well-designed trial that selects participants by status and follows them long enough would settle most of what is left in doubt. Until then, claims that supplementation controls diabetes should be treated as unproven, and claims that it is useless as equally premature.

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## 9. Conflict of Interest

The authors declare no conflict of interest.

## 10. Author Contributions

Q.F. conceived the review and wrote the sections on biology and observational evidence. M.T. wrote the sections on supplementation trials and measurement. A.B. wrote the methods, discussion and conclusion. All authors read and approved the final text.

## 11. Ethics Statement

This is a review of published literature. No participants were recruited and no ethical approval was required.

## 12. Data Availability

No new data were generated. All sources are cited in the reference list.

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