REVIEW

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Role of vitamin D in insulin resistance

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ABSTRACT

There is plenty of evidence in the literature that vitamin D is essential for calcium homeostasis for optimal skeletal health. Type 2 diabetes mellitus is a syndrome with major long-term negative consequences. Efforts have been made to find innovative approaches for diabetes prevention and treatment, and a recent focus has been on vitamin D supplementation. The aim of this review was to evaluate the effect of vitamin D on insulin resistance.

Keywords
Vitamin D
Insulin resistance
Type 2 diabetes mellitus

Introduction

There is plenty of evidence in the literature that vitamin D is essential for calcium homeostasis for optimal skeletal health. Vitamin D status is best determined by measuring serum 25-hydroxy D (25(OH)D); a level above 30 ng/ml contributes to optimal calcium absorption, prevention of falls and fracture prevention [1]. Type 2 diabetes mellitus is a syndrome with major long-term negative consequences. It is characterized by hyperglycaemia, hyperlipidaemia and other metabolic abnormalities resulting in neurological and small- and large-blood vessel complications. Efforts have been made to find innovative approaches for diabetes prevention and treatment, and a recent focus has been on vitamin D supplementation. Experimental and epidemiological studies have suggested calcium and vitamin D supplementation has beneficial effects in reducing the risk of developing diabetes. There are many research studies in the literature showing evidence of a relationship between both type 1 and type 2 diabetes mellitus and vitamin D, as well as the beneficial effects of vitamin D supplementation in reducing the risk of diabetes and insulin resistance. Moreover, there is an inverse correlation between serum 25(OH)D levels and cardiovascular diseases, metabolic syndrome, and their complications, such as glucose intolerance, hypertension, obesity, insulin resistance, ischaemic heart disease and stroke [2–5]. The aim of this review was to evaluate the effect of vitamin D on insulin resistance.

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Material and methods

A systematic search strategy was developed to identify randomized controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 1996 through April 2018) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK). The terms 'vitamin D', 'insulin resistance', 'glycemia' and 'diabetes mellitus' were incorporated into an electronic search strategy that included the Dickersin filter for randomized controlled trials [6]. It was also discovered that some reports have only been published in Japanese. To avoid problems and limitations with the translation of these reports, it was decided to perform this review by including only studies published in English. The bibliographies of all identified randomized trials and review articles

were reviewed to look for additional studies of interest. We reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions evaluated and outcome measured. Studies were required to be trials evaluating vitamin D effects at any dosage on insulin resistance. The following data were abstracted onto standardized case report forms: authors; year of publication; country of study; source of funding; study goal; means of randomization and blinding; duration of treatment; treatment characteristics; sex; quantity of and reasons for subjects withdrawing from the study; systolic and diastolic blood pressure and ages of the treatment and control groups; outcomes; and adverse event data. A validated, three-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomization (0–2 points), double-blinding (0–2 points) and account for withdrawals (1 point). Scores ranged between 0 and 5, a score of 3 indicated a study of high quality [7], and study selection was restricted to randomized, controlled trials to ensure the inclusion of only high-quality evidence.

Results

Upreti *at al* [8] enrolled 60 patients with coexisting type 2 diabetes mellitus and hypovitaminosis D and supplemented them with oral vitamin D or microcrystalline cellulose for 6 months. Subjects' glycated haemoglobin (HbA1c) and vitamin D levels were monitored at the beginning and end of the study, while fasting plasma glucose (FPG) and post-prandial glucose (PPG) were measured each month.

Patients treated with vitamin D showed a significant decrease in mean HbA1c levels (from 7.29% to 7.02%; p=0.01), mean FPG levels (from 131.4 to 102.6 mg/dl; p=0.04) and mean PPG levels (from 196.2 to 135.0 mg/dl; p<0.001). Moreover, significant improvements in systolic as well as diastolic blood pressure and total cholesterol were also noted in patients treated with vitamin D, while the improvement for LDL cholesterol tended towards significance (p=0.05). This trial showed that supplementation with vitamin D led to improvement in parameters of glycaemic control in patients with type 2 diabetes mellitus with concurrent hypovitaminosis D. This study also showed that correction of vitamin D deficiency/insufficiency led to improvement in cardiovascular risk factors such as blood pressure and lipid parameters [8].

Gao *et al* [9] conducted a 4-year follow-up study including 490 participants who were free of prediabetes and type 2 diabetes mellitus at baseline and had complete data by the time of follow-up examinations. Glucose, insulin and 25(OH)D levels were measured at baseline and 4 years later. Prediabetes and type 2 diabetes mellitus were identified using the results obtained from an oral glucose tolerance test (OGTT). Over a 4-year follow-up period, 95 patients (48.5%) developed prediabetes and 31 (15.8%) individuals developed diabetes. Low 25(OH)D status was significantly associated with the risk of developing prediabetes (OR 3.01, 95% CI 1.50 to 6.06; p=0.002) and type 2 diabetes mellitus (OR 5.61, 95% CI 1.73 to 18.27; p=0.004) after adjustment for multiple potential confounders. In a multiple linear regression analysis, low baseline levels of 25(OH)D were an independent predictor of increased insulin resistance over a 4-year period (p<0.05). This prospective study suggests that low 25(OH)D levels might have contributed to the incidence of prediabetes or type 2 diabetes mellitus in Chinese individuals.

Lithgow *et al* [10] evaluated if there was a synergistic metabolic effect of high-intensity intermittent training and vitamin D supplementation on glycaemic control. A total of 20 male and female participants (age 34±9 years; BMI 31.4±2.8 kg/m^2) completed 6 weeks of high-intensity intermittent training, and were randomized to ingest 100 μg/day of vitamin D3 or placebo. Response to an OGTT was determined at baseline and at 72 hours post-intervention. Glucose tolerance was improved as a result of the high-intensity intermittent training intervention, shown by a reduction in glucose and insulin concentrations during the OGTT, accompanied by a decrease in glucose (from 829±110 to 786±139 mmol/h/l; p=0.043) and insulin (from 8101±4755 to 7024±4489 mU/h/l; p=0.049) area under the curve (AUC). Supplementation increased 25-hydroxy-vitamin D3 concentration by 120% to a sufficiency status (p<0.001). However, the consumption of vitamin D3 seemed to attenuate the glucose response during an OGTT. Triglyceride content was lowered following the intervention (p=0.025). There was no effect of the intervention on insulin sensitivity (IS) indices: ISIMatsuda and HOMA-IR. The study demonstrates that high-intensity intermittent training improves glucose tolerance in non-diabetic overweight and obese adults; however, vitamin D3 supplementation did not offer any additional positive effects on the measured indices of metabolic health.

Conclusions

The dose of vitamin D which is sufficient to achieve non-skeletal benefits still remains unclear. In terms of intervention, daily doses of more than 2,000 IU/day were consistently associated with a higher post-test vitamin D status and larger improvement in glycaemic indices. Some observational studies showed that supraphysiological dosing with vitamin D could be harmful; however, the most common supplementation dose (2,000 IU/day) was much lower than that, as well as than the debated dosing required for efficacy which is 4,000–5,000 IU/day [11, 12]. Under these conditions, the benefits of higher doses seemed reasonable since high doses increased the chances of correcting vitamin D deficiency or achieving favourable levels of serum 25(OH)D, confirmed by relatively higher 25(OH)D levels in the high-dose subgroup after intervention (31.6 *versus* 30 ng/ml in the low-dose subgroup). The impact of intervention duration was more ambiguous, contrary to the findings of Mirhosseini *et al* and Lee *et al* that longer durations of supplementation were associated with larger improvements in glycaemic control, which was possibly due to the 2–3-month lifespan of HbA1c [11, 13].

Regarding the possible mechanism governing the relationships between vitamin D and diabetes, there is evidence that β-cells contain vitamin D receptors, and that 25(OH)D stimulates insulin release. Insulin secretion is calcium dependent and calcium homeostasis depends on vitamin D: vitamin D supplements improve insulin release in response to oral glucose load and reduce free fatty acid levels. Sedentary and obese people get less sun exposure and thus have less vitamin D.

REFERENCES

1. Laird E, Ward M, McSorley E, Strain JJ, Wallace J (2010) Vitamin D and bone health: potential mechanisms. Nutrients 2(7):693–724
2. Schottker B, Herder C, Rothenbacher D, Perna L, Muller H, Brenner H (2013) Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. Eur J Epidemiol 28(3):267–275
3. Pittas AG, Sun Q, Manson JE, Dawson-Hughes B, Hu FB (2010) Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. Diab Care 33(9):2021–2023
4. Mattila C, Knekt P, Mannisto S, Rissanen H, Laaksonen MA, Montonen J *et al* (2007) Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diab Care 30(10):2569–2570
5. Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Shaw JE, Zimmet PZ *et al* (2011) Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). Diab Care 34(5):1133–1138
6. Dickersin K, Scherer R, Lefebvre C (1994) Identifying relevant studies for systematic reviews. BMJ 309:1286–1291
7. Jadad AR, Moore RA, Carroll D *et al* (1996) Assessing the quality of randomized controlled trials: is blinding necessary? Control Clin Trials 17:1–12
8. Upreti V, Maitri V, Dhull P, Handa A, Prakash MS, Behl A (2018) Effect of oral vitamin D supplementation on glycemic control in patients with type 2 diabetes mellitus with coexisting hypovitaminosis D: a parellel group placebo controlled randomized controlled pilot study. Diabetes Metab Syndr 12(4):509–512
9. Gao Y, Zheng T, Ran X, Ren Y, Chen T, Zhong L *et al* (2018) Vitamin D and incidence of prediabetes or type 2 diabetes: a four-year follow-up community-based study. Dis Markers 2018:1926308
10. Lithgow HM, Florida-James G, Leggate M (2018) The combined effect of high-intensity intermittent training and vitamin D supplementation on glycemic control in overweight and obese adults. Physiol Rep 6(9):e13684
11. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM (2017) The effect of improved serum 25-hydroxyvitamin D status on glycemic control in diabetic patients: a meta-analysis. J Clin Endocrinol Metab 102:3097–3110
12. Nigil HN, Anton A, John J, Mittal M (2015) Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies. J Diabetes Metab Disord 14:3
13. Lee CJ, Iyer G, Liu Y, Kalyani RR, Bamba N, Liqon CB *et al* (2017) The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: a systematic review and meta-analysis of intervention studies. J Diabetes Complicat 31:1115–1126