Medicine®

OPEN

Efficacy of vitamin D supplementation on glycemic control in type 2 diabetes patients
A meta-analysis of interventional studies

Zhiwei Hu, MM, Jin'an Chen, MM, Xinjuan Sun, PhD, Lei Wang, MM, Aiping Wang, MD*

Abstract
Background: Conflicting evidence exists on the effect of vitamin D supplementation on glucose metabolism in subjects with type 2 diabetes (T2D). Therefore, this meta-analysis focuses on the relationship between vitamin D intervention and glycaemic control in subjects with T2D.

Methods: We reviewed available randomized controlled trials (RCTs) studies from the establishment time of each database to March 31, 2018. Stata 13.0 software was used to evaluate the included literature.

Results: Finally, a total of 19 RCT studies involving 747 intervention subjects and 627 placebo controls were included in this meta-analysis. Meta-analysis results showed that compared with the control group, the short-term vitamin D supplementation group had a decline in hemoglobin A1c (HbA1c), insulin resistance, and insulin. The Standard Mean Difference (SMD) (95% CI [95% confidence interval]) of HbA1c, insulin resistance, and insulin were -0.17 (-0.29, -0.05), -0.75 (-0.97, -0.53), -0.57 (-0.78, -0.35), respectively with all P value $<.05$. But there were no significant differences in long-term follow-up vitamin D intervention.

Conclusion: Vitamin D supplementation in T2D patients can improve HbA1c, insulin resistance, and insulin in short-term intervention, suggesting that vitamin D can be considered as a therapeutic agent along with the other treatments for T2D.

Abbreviations: 95% CI = 95% confidence interval, FBG = fasting blood glucose, HbA1c = hemoglobin A1c, HOMA-IR = homeostasis model assessment-insulin resistance, PPAR-δ = peroxisome proliferator activated receptor, RCT = randomized controlled trial, SMD = Standard Mean Difference, T2D = type 2 diabetes.

Keywords: glycaemic control, meta-analysis, RCT, type 2 diabetes, vitamin D

1. Introduction

Type 2 diabetes (T2D) is a public health challenge all over the world. By the end of 2015, a total of 392 million people suffer from T2D worldwide.[1] T2D is a long-term metabolic disorder which is characterized by the relative lack of insulin, insulin resistance, and high blood glucose.[2] It has been well known that T2D is a major risk factor for premature mortality and adverse complications such as blindness, stroke, heart attack, amputation, and kidney failure.[3]

Over the past few decades, series studies have evaluated the association of circulating Vitamin D concentrations with T2D risk and yielded a tight relationship between them, although the

findings remain inconsistent.[4] Scragg et al reported an inverse association between vitamin D status and diabetes,[5] however no significant relationship of vitamin D status with fasting glucose and insulin was found in another cross-sectional study.[6] Interestingly, 2 women nested case–control studies observed inconclusive results between plasma 25-(OH)D levels and risk of incident T2D.[7,8] Numerous prospective cohort studies have demonstrated that higher vitamin D status was associated with decreased risk of T2D.[9–11] These population epidemiological evidence indicated that Vitamin D plays an important role in T2D and sequent diseases. Therefore, the researches on the positive preventive effect of vitamin D supplement on diabetes were widely carried out.

Alcubierre et al suggested that vitamin D deficiency was significantly associated with lower quality of life, as well as with lower satisfaction with diabetes treatment.[12] Recently, a randomized controlled trials (RCTs) study showed that vitamin D supplementation not only reduced blood glucose in T2D patients but also increased insulin sensitivity.[13] Besides, it has also been suggested that the intake of vitamin D was inversely associated with the development of T2D complications.[14] On the other hand, there was a lack of correlation between the use of vitamin D and insulin secretion rate neither and hemoglobin A1c (HbA1c) in T2D patients.[15] RCTs studies reported a discrepancy between vitamin D supplementation and effeteness of T2D treatment. These inconsistent results might be partly due to small number of eligible participants. To systematically evaluate the effects of vitamin D supplementation on fasting blood glucose (FBG), insulin, HbA1c, and homeostasis model assessment-insulin resistance (HOMA-IR) in T2D patients, this RCT meta-analysis was conducted.

2. Materials and methods

Since this study is a meta-analysis of previously published studies, the ethical approval and patient consent are not required.

2.1. Search strategy

Comprehensive searches for eligible trials were performed by an electronic search of the PubMed, Elsevier database, Wiley database, Springer Link, and the Cochrane library. Searched the Title/ Abstract using the following terms:("Vitamin D" or "Cholecalciferol" or "calcitriol" or "Vitamin D2" or "Vitamin D3") and ("Diabetes" or "T2D" or "hyperglycemia"). The time searched was from the establishment time of each database to March 31, 2018. All of the studies were limited to English language.

2.2. Eligibility and exclusion criteria

Eligibility criteria were set as follows:

(1) all studies had to be a RCT design;
(2) studies should provide at least one of the following outcomes (FBG or insulin or HbA1c or insulin resistance);
(3) insulin resistance estimated by HOMA-IR and HOMA-IR = (glucose, [mmol/L] x insulin [mU/L])/22.5[16]
(4) data description was mean ± SD;
(5) cases were T2D patients;
(6) the intervention group was treated with Vitamin D, while the control group was given placebo.

Exclusion criteria were set as follows:

(1) reviews, abstracts or animal studies;
(2) incompleteness of information data;
(3) error of statistical methods
(4) follow-up less than 2 months;
(5) cases had gestational diabetes, post partum diabetes, diabetic nephropathy, type 1 diabetes and high-risk population of diabetes.

2.3. Data collection

Two investigators independently scanned titles or abstracts to exclude studies which failed to meet the mentioned criteria and then obtained, reviewed and extracted the full-text reports for further assessment. Disagreements were resolved by consensus. Detailed data of eligible trials such as study design, participants' information, methodological evaluation, intervention outcomes, and adverse event reports were extracted.

2.4. Statistical analysis

This meta-analysis adopted stata13.0 software for statistical analysis. SD $(\Delta) = [SD^2$ (baseline)+SD^2 (final) $-2 \times 0.5 \times SD$ (baseline)+SD^2 (final)$]^{1/2}$.[17] Q test and the I^2 index was used to assess the statistical heterogeneity. If there was no statistically significant heterogeneity ($P > .1$ and $I^2 < 50\%$), a pooled effect was calculated with a fixed-effects model, whereas a
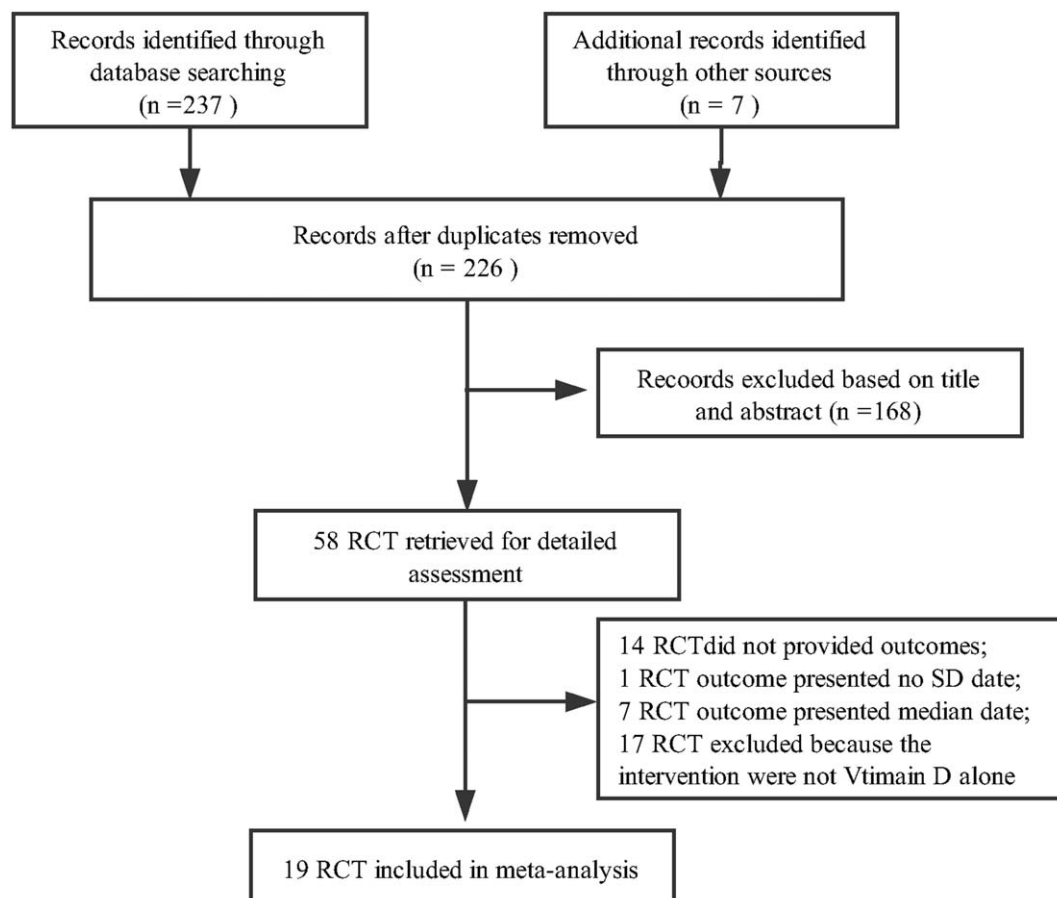

Figure 1. Flow chart of study selection.

random-effects model was employed on the contrary ($P <.1$ or $I^2 > 50\%$). The strength of relationship between vitamin D supplementation and outcomes were by the value of the Standard Mean Difference (SMD) and 95% confidence interval (95%CI).

3. Results

3.1. Study characteristics

In the primary search, 244 articles were retrieved, thereby 58 articles to further screening after reviewed on title and abstract. Finally, 19 independent studies accorded with conditions through full text reviewed.[13,18–35] The detail omitted records were presented in the Figure 1. The study follow-up time with more than 6 months was considered as long-term study and those less than 6 months was considered as short-term study. All studies were used the JADAD scale to assessed the quality.[36] Research in 3 points or more believed that the quality is high. The characteristics and scores of eligible studies were summarized in Supplement Table1, http://links.lww.com/MD/C911.

3.2. Quantitative synthesis

In this meta-analysis, we did not observe a significant FBG change in vitamin D supplement intervention group. After a subgroup analysis by follow-up time, the result remained no statistical difference. The data was shown in Supplementary Figure 1, http://links.lww.com/MD/C911.

No significant difference was noted in HbA1c change between the intervention group and the placebo group. Whereas after a subgroup analysis, we found that the level of HbA1c decreased significantly in the short-term follow-up intervention group and the SMD (95% CI) was $-0.17\,(-0.29, -0.05)$ with $P = .007$. The data was shown in Figure 2.

In the 11 studies, there was significant decrease in HOMA-IR with vitamin D supplementation. In the subgroup analysis, we found that the level of HOMA-IR decreased significantly in the short-term follow-up intervention group and the SMD (95% CI) was $-0.75\,(-0.97, -0.53)$ with $P <.001$. The data was shown in Figure 3.

Similarly, we observed insulin change in the vitamin D supplementation group. After subgroup analysis, we found that the level of insulin reduced significantly in the short-term
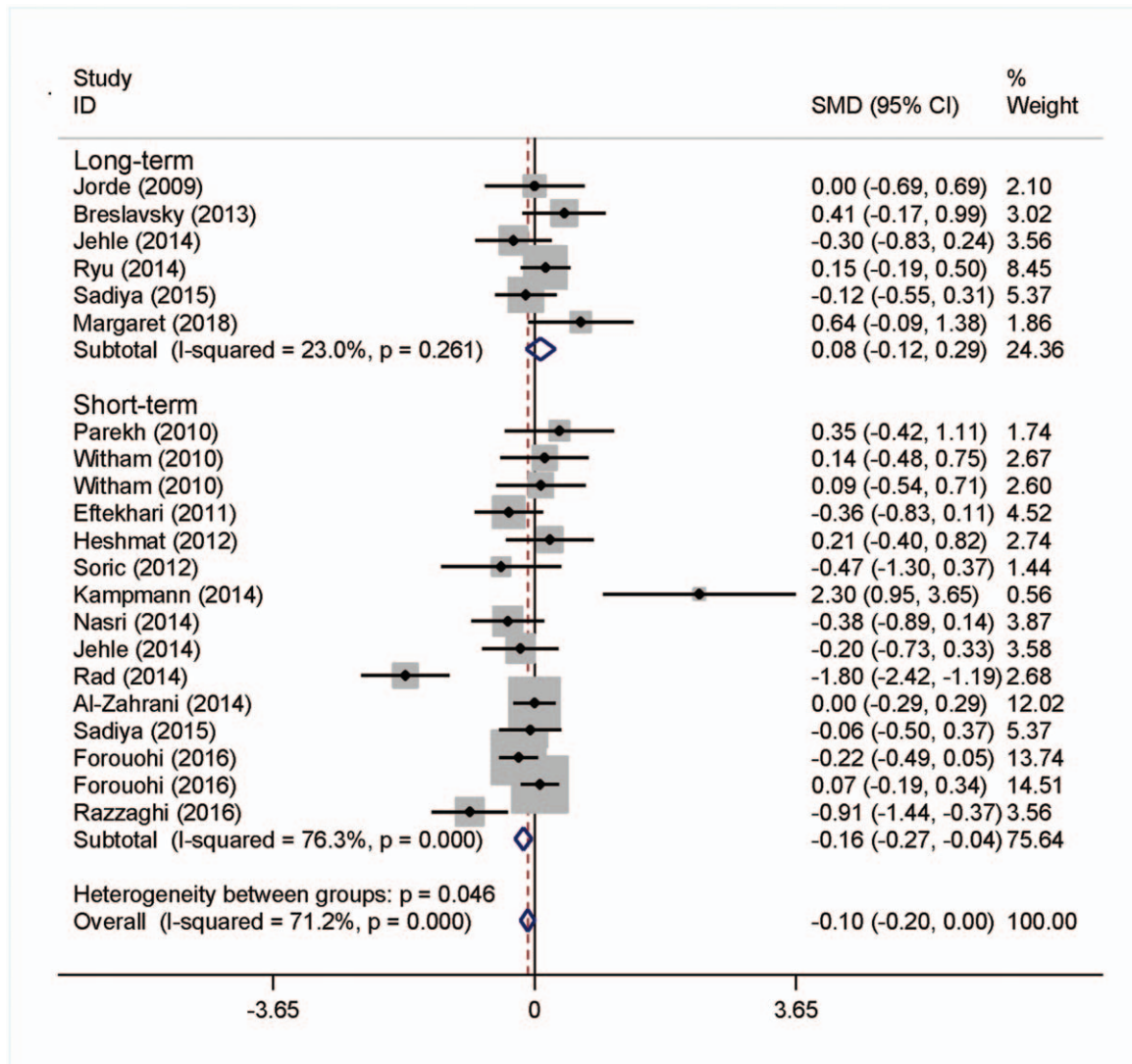

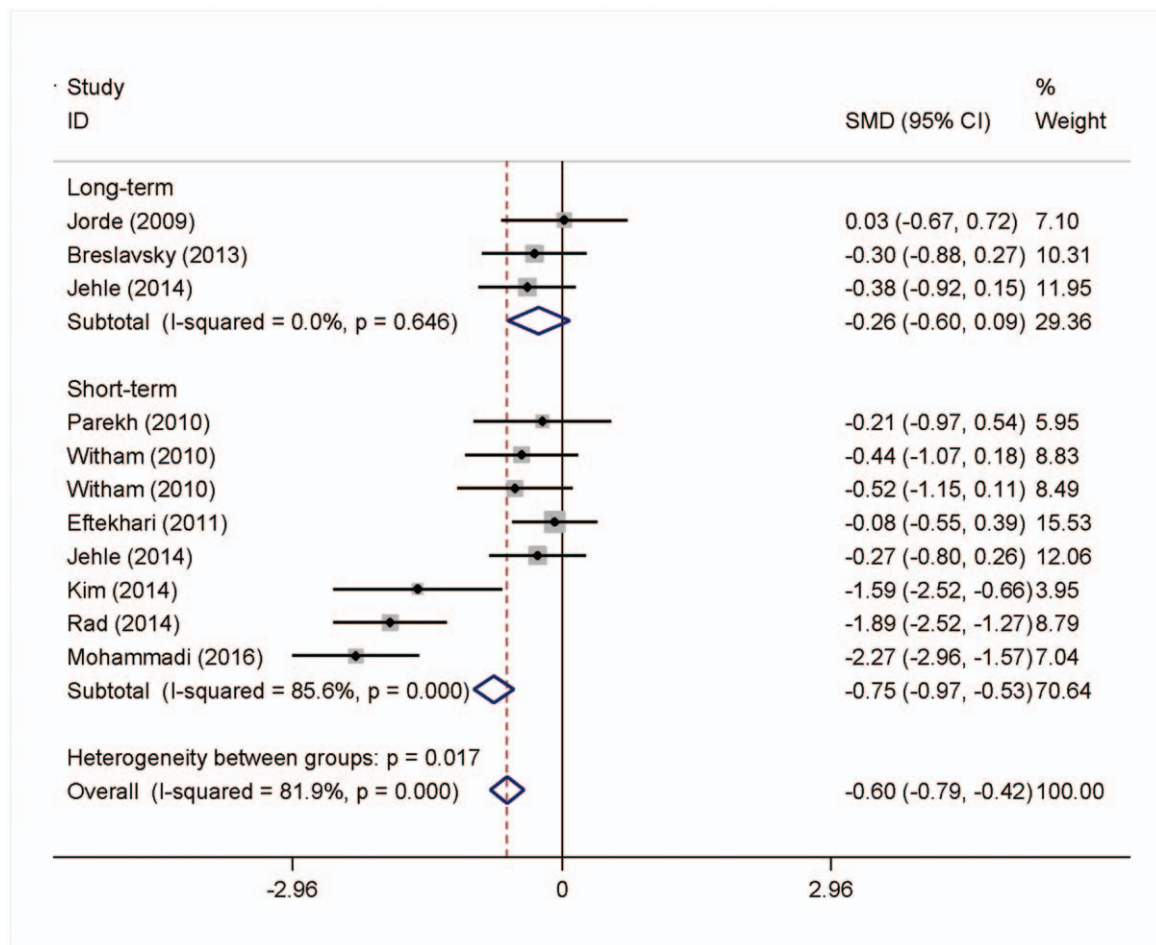Figure 2. Meta-analysis of effects on HbA1c.

Figure 3. Meta-analysis of effects on insulin resistance.

follow-up vitamin D supplementation group and the SMD (95% CI) was −0.57 (−0.78, −0.35) with $P < .001$. The data was shown in Figure 4.

3.3. Publication bias and sensitivity analysis

Egger test was applied to assess the included literature publication bias in this study and no significant publication bias was found, the Egger test P value of the FBG, HbA1c, HOMA-IR, and insulin were 0.922, 0.450, 0.149, and 0.082, respectively.

Results showed high heterogeneity in HbA1c, HOMA-IR, and insulin except FBG (Figures 2–4, Supplementary Figure 1, http:// links.lww.com/MD/C911), then sensitivity analysis was carried out to find the sources of heterogeneity. After removing 1 study at a time, we found that the Rad et al study change the pooled HbA1c SMD quite big. The heterogeneity among the studies was clearly reduced ($I^2 = 57\%$) and the pooled SMD became no longer significant ($P = .114$).

Sensitivity analysis results demonstrated that most of the HOMA-IR heterogeneity belonged to the study of Rad et al and Mohammadi et al. The heterogeneity was reduced after exclusion of the 2 studies ($I^2 = 42\%$) and the pooled SMD remained significant.

4. Discussion

In this meta-analysis of prospective RCT designed for glycaemic control outcomes in subjects with T2D, we found that vitamin D supplementation prevented the increase in plasma HbA1c, insulin resistance and insulin in the subgroup of subjects with short-term follow-up intervention but had no apparent effect among those with long-term follow-up intervention. No effect of supplementation on plasma FBG among either subgroup was observed.

HbA1c is caused by continuous slow non-enzymatic glycosylation of hemoglobin due to hyperglycemia. The UK Prospective Diabetes Study demonstrated that HbA1c is a gold standard for the evaluation of glycemic control in the control of diabetes, with a 1% reduction, a 14% reduction in related cardiovascular events.[37] George et al have conducted a meta-analysis to evaluate the effect of vitamin D on glycaemic control and insulin resistance.[38] The paper found a small improvement on FBG and insulin resistance but no beneficial effect was seen on HbA1c. However, this meta-analysis included both impaired FBG patients and T2D patients. In our meta-analysis, we observed vitamin D supplementation prevented the increase in plasma HbA1c, suggesting that vitamin D is beneficial to reduce or delay the occurrence and development of diabetic complications. These inconsistent results might be due to our increased updated studies.
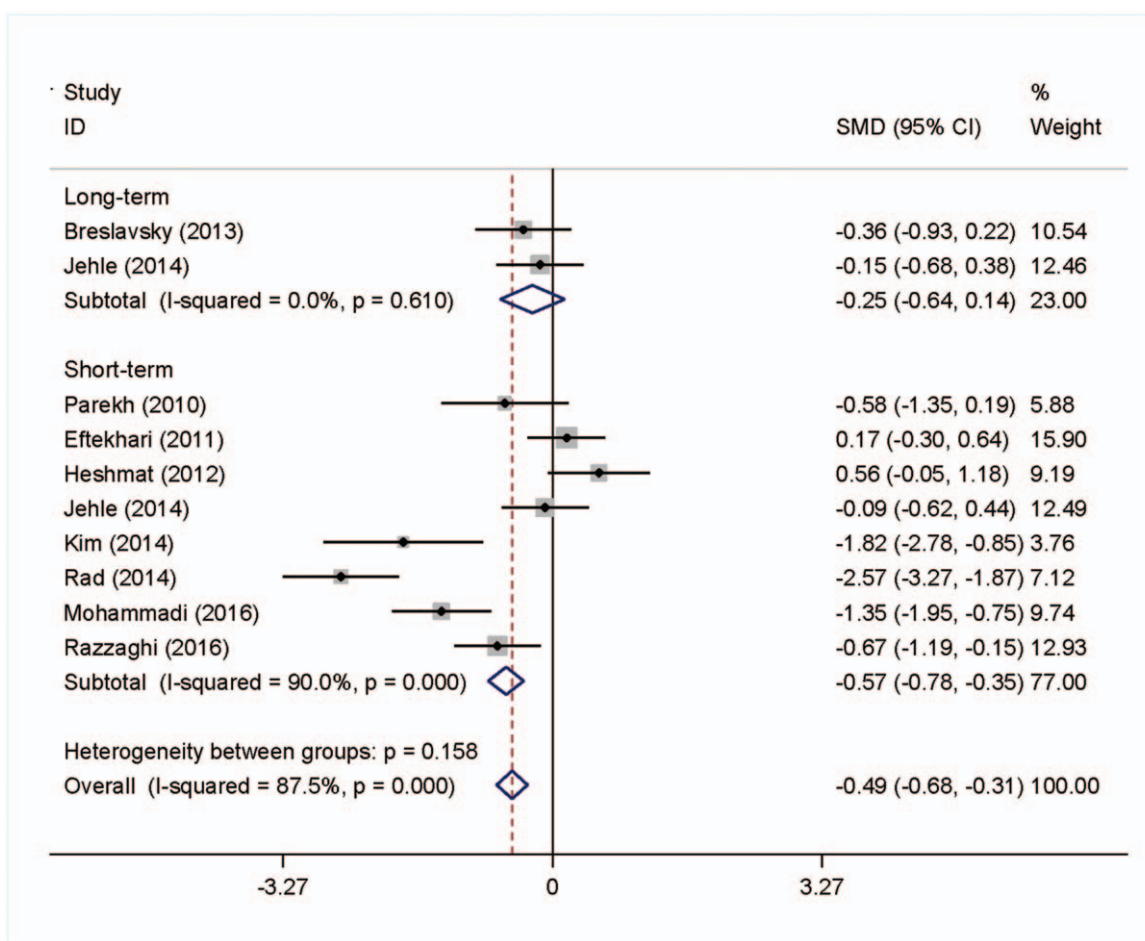
Figure 4. Meta-analysis of effects on insulin secretion.

HOMA-IR was an important factor in the development of diabetes mellitus, and there was a significant positive correlation between them.[39] The decreased sensitivity of insulin target tissues to insulin is called IR and most patients with T2D have combined IR.[2] The level of blood glucose and insulin secretion can often reflect the sensitivity of insulin indirectly. At the same time, blood glucose has not been effectively controlled, which will further stimulate the β-cells to synthesize more insulin.[40] Our results showed a significant decrease in insulin and HOMA-IR levels in vitamin D supplementation group. Insulin secretion is a calcium-dependent process. L-type calcium channels on islet β-cells are activated by activated vitamin D which then regulates calcium levels, initiates insulin signaling, and promotes insulin release.[41] Vitamin D deficiency can be accompanied by a decrease in plasma calcium concentration, which in turn causes a secondary increase in calcium levels, affecting insulin signal transduction, interfering with insulin release and disrupting islet β cell function.[42] Fatty acid metabolism in skeletal muscle and adipose tissue is regulated by peroxisome proliferator-activated receptor (PPAR-δ) and PPAR-δ has a certain regulatory effect on IR. Vitamin D can directly activate PPAR-δ expression, thereby improving IR.[43]

Studies have shown that vitamin D deficiency is associated with the development of T2D, T2D nephropathy, T2D microvascular or macrovascular disease, diabetic retinopathy, and diabetic peripheral neuropathy.[44–48] In an 11-year cohort follow-up study, baseline vitamin D levels were negatively correlated with the development of T2D.[49] The genetic polymorphisms of vitamin D binding protein and vitamin D receptor are associated with genetic susceptibility to T2D. In a Japanese study, significant differences in insulin and IR between different vitamin D binding protein genotypes were found in adults with normal glucose tolerance.[50] Therefore, the present study further supports these work and indicate that vitamin D supplementation improves IR in patients with T2D in the short term.

In the subgroup analysis, there was no apparent decreased in plasma HbA1c, HOMA-IR and insulin with long-term follow-up intervention. This may be due to random errors in the study itself. On the other hand, the fact that the prolonged duration of T2D or gradually worsen with the course of T2D may help to explain the result.[51] Moreover, it has been shown that compared with FBG, the 2 hours postprandial blood glucose contributes more to HbA1c,[52] which may be an important reason for the difference HbA1c between vitamin D supplementation group and the control group, but no statistical significance in FBG.

Sensitivity analysis suggested that the major sources of heterogeneity in results were due to the studies of Rad et al[30] and Mohammadi et al.[33] The other causes such as ethnic, the health status of patients and quality of the studies may lead to the heterogeneity.

There are some limitations in this study. First, the long-term follow-up studies included are few. Second, we did not consider

the vitamin D intake dose variations in the include studies which may generate some heterogeneity and the inconsistency in the supplemental dose of vitamin D may cause a certain shift in the combined values. Finally, although the heterogeneity of the literature was circumvented, heterogeneity still existed. Of course, based on the perspective of evidence-based medicine, this study shows that vitamin D supplementation can play an important role in controlling blood glucose and improving IR.

In summary, vitamin D supplementation in T2D patients can improve HbA1c, insulin resistance, and insulin in short-term intervention, but the impact on the FBG is not significant. Therefore, vitamin D can be considered as a therapeutic agent along with the other treatments for T2D.

Author contributions

Conceptualization: Aiping Wang.
Data curation: Jinan Chen, Lei Wang.
Methodology: Xinjuan Sun.
Writing – original draft: Zhiwei Hu.

References

[1] Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1545–602.

[2] Muoio DM, Newgard CB. Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:193–205.

[3] Lotfy M, Adeghate J, Kalasz H, et al. Chronic complications of diabetes mellitus: a mini review. Curr Diabetes Rev 2017;13:3–10.

[4] Mezza T, Muscogiuri G, Sorice GP, et al. Vitamin D deficiency: a new risk factor for type 2 diabetes. Ann Nutr Metab 2012;61:337–48.

[5] Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2813–8.

[6] Dalgård C, Petersen MS, Weihe P, et al. Vitamin D status in relation to glucose metabolism and type 2 diabetes in septuagenarians. Diabetes Care 2011;34:1284–8.

[7] Pittas AG, Sun Q, Manson JE, et al. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. Diabetes Care 2010;33:2021–3.

[8] Robinson JG, Manson JAE, Larson J, et al. Lack of association between 25(OH)D levels and incident type 2 diabetes in older women. Diabetes Care 2011;34:628–34.

[9] Claudia G, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years. Diabetes Care 2011;34:1133–8.

[10] Liu E, Meigs JB, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. Am J Clin Nutr 2010;91:1627–33.

[11] Liu E, Mckeown NM, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and change in fasting plasma glucose in the framingham offspring study. Eur J Clin Nutr 2011;66:139–41.

[12] Alcubierre N, Castelblanco E, Martínez-Alonso M, et al. Vitamin D deficiency is associated with poorer satisfaction with diabetes-related treatment and quality of life in patients with type 2 diabetes: a cross-sectional study. Health Qual Life Outcomes 2018;16:44–51.

[13] Rad EY, Djalali M, Koohdani F, et al. The effects of vitamin D supplementation on glucose control and insulin resistance in patients with diabetes type 2: a randomized clinical trial study. Iranian J Public Health 2014;43:1651–6.

[14] Mattila C, Knekt P, Männistö S, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 2007;30:2569–70.

[15] Angellotti E, D'Alessio D, Dawson-Hughes B, et al. Vitamin D supplementation in patients with type 2 diabetes: the vitamin D for established type 2 diabetes (DDM2) study. J Endocrine Soc 2018;2:310–21.

[16] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.

[17] Follmann D, Elliott P, Suh I, et al. Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 1992;45:769–73.

[18] Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. Eur J Nutr 2009;48:349–54.

[19] Parekh D, Sarathi V, Shivane VK, et al. Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes mellitus. Endocr Pract 2010;16:600–8.

[20] Witham MD, Dove FJ, Dryburgh M, et al. The effect of different doses of vitamin D 3 on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia 2010;53:2112–9.

[21] Eftekhari MH, Akbarzadeh M, Dabbaghmanesh MH, et al. Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients. Asia Pacific J Clin Nutr 2011;20:521–6.

[22] Heshmat R, Tabatabaeimalazy O, Abbaszadehahranjani S, et al. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. Daru J Pharma Sci 2012;20:10–5.

[23] Soric MM, Renner ET, Smith SR. Effect of daily vitamin D supplementation on HbA1c in patients with uncontrolled type 2 diabetes mellitus: A pilot study. J Diabetes 2012;4:104–5.

[24] Shargorodsky* M, Gavish D. Effect of high doses of vitamin D on arterial properties, adiponectin and glucose homeostasis in type 2 diabetic patients. Clin Nutr 2013;32:970–5.

[25] Kampmann U, Mosekilde L, Juhl C, et al. Effects of 12 weeks high dose vitamin D3 treatment on insulin sensitivity, beta cell function, and metabolic markers in patients with type 2 diabetes and vitamin D insufficiency - a double-blind, randomized, placebo-controlled trial. Metab Clin Exp 2014;63:1115–24.

[26] Nasri H, Behradmanesh S, Maghsoudi AR, et al. Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. J Renal Inj Prev 2014;3:31–4.

[27] Jehle S, Lardi A, Felix B, et al. Effect of large doses of parenteral vitamin D on glycaemic control and calcium/phosphate metabolism in patients with stable type 2 diabetes mellitus: a randomised, placebo-controlled, prospective pilot study. Swiss Med Wkly 2014;144:w13942–13951.

[28] Kim HJ, Kang CK, Park H, et al. Effects of vitamin D supplementation and circuit training on indices of obesity and insulin resistance in T2D and vitamin D deficient elderly women. J Exerc Nutrition Biochem 2014;18:249–57.

[29] Ryu OH, Lee S, Yu J, et al. A prospective randomized controlled trial of the effects of vitamin D supplementation on long-term glycemic control in type 2 diabetes mellitus of Korea. Endocrine J 2014;61:167–76.

[30] Al-Zahrani MK, Elnasieh AM, Alenezi FM, et al. A 3-month oral vitamin D supplementation marginally improves diastolic blood pressure in Saudi patients with type 2 diabetes mellitus. Int J Clin Exp Med 2014;7:5421–8.

[31] Sadiya A, Ahmed SM, Carlsson M, et al. Vitamin D supplementation in obese type 2 diabetes subjects in Ajman, UAE: a randomized controlled double-blinded clinical trial. Eur J Clin Nutr 2015;69:707–11.

[32] Mohammad MS, Ahmad ES, Sedighah S, et al. The effects of vitamin D supplementation on adiponectin level and insulin resistance in first-degree relatives of subjects with type 2 diabetes: a randomized double-blinded controlled trial. Electron Phys 2016;8:2849–54.

[33] Forouhi NG, Menon RK, Sharp SJ, et al. Effects of vitamin D2 or D3 supplementation on glycaemic control and cardiometabolic risk among people at risk of type 2 diabetes: results of a randomized double-blind placebo-controlled trial. Diabetes Obes Metab 2016;18:392–400.

[34] Razzaghi R, Pourbagheri H, Momen-Heravi M, et al. The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. J Diabetes Complicat 2016;31:766–72.

[35] Lo MC, Abushamat L, Mramba LK. Effect of treating vitamin D deficiency in uncontrolled type 2 diabetes: a randomized, placebo-controlled study. Am J Ther 2018;2:1–11.

[36] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary. Control Clin Trials 1996;17:1–2.

[37] Listed N. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.

[38] George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabetic Med 2012;29:e142–50.

[39] Ma L, Yun L. Cognitive function and insulin resistance in elderly patients with type 2 diabetes. Neurol Res 2017;39:259–63.

[40] Acevedonegrete AP, Porchia LM, Gonzalezmejia ME, et al. The impact of parental history of type 2 diabetes on hyperinsulinemia and insulin resistance in subjects from central Mexico. Diabetes Metabol Syndr 2017;7:1–6.

[41] Jung SR, Reed BJ, Sweet IR. A highly energetic process couples calcium influx through L-type calcium channels to insulin secretion in pancreatic beta-cells. Am J Physiol Endocrinol Metabol 2009;297:E717–27.

[42] Kamycheva E, Jorde R, Figenschau Y, et al. Insulin sensitivity in subjects with secondary hyperparathyroidism and the effect of a low serum 25-hydroxyvitamin D level on insulin sensitivity. J Endocrinol Invest 2007;30:126–32.

[43] Hoseini R, Damirchi A, Babaei P. Vitamin D increases PPAR expression and promotes beneficial effects of physical activity in metabolic syndrome. Nutrition 2016;36:54–9.

[44] Haroon NN, Anton A, John J, et al. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies. J Diabetes Metabol Disord 2015;14:1–11.

[45] Alcubierre N, Valls J, Rubinat E, et al. Vitamin D deficiency is associated with the presence and severity of diabetic retinopathy in type 2 diabetes mellitus. J Diabetes Res 2015;2015:1–7.

[46] Herrmann M, Sullivan DR, Veillard AS, et al. Serum 25-hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. Diabetes Care 2014;38:521–8.

[47] Aksoy H, Akçay F, Kurtul N, et al. Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. Clin Biochem 2000;33:47–51.

[48] Shehab D, Aljarallah K, Mojiminiyi OA, et al. D deficiency play a role in peripheral neuropathy in Type 2 diabetes. Diabetic Med 2012;29:43–9.

[49] Grimnes G, Emaus N, Joakimsen RM, et al. Baseline serum 25-hydroxyvitamin D concentrations in the Tromsø Study 1994-95 and risk of developing type 2 diabetes mellitus during 11 years of follow up. Diabetic Med 2010;27:1107–15.

[50] Hirai M, Suzuki S, Hinokio Y, et al. Variations in vitamin D-binding protein (group-specific component protein) are associated with fasting plasma insulin levels in Japanese with normal glucose tolerance. J Clin Endocrinol Metabol 2000;85:1951–3.

[51] Gambineri A, Patton L, Altieri P, et al. Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. Diabetes 2012;61:2369.

[52] Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. JAMA J Am Med Assoc 2013;310:948–59.