Effect of vitamin D supplementation on glucose homeostasis and islet function in vitamin D deficient or insufficient diabetes and prediabetes: a systematic review and meta-analysis

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(Received 3 October, 2020; Accepted 25 October, 2020; Published online 7 May, 2021)

Objective of the present study was to evaluate the effect of vitamin D supplementation on glucose homeostasis, islet function, and diabetes progress. Literatures were searched via electronic databases, websites, and previous reviews from the earliest available time to the end of May 2020. Randomized controlled trials initially designed for diabetes and prediabetes with 25-dihydroxyvitamin D [25(OH)D]<30 ng/ml were included. All data were analyzed and presented based on the Cochrane guidelines and PRISMA guidelines. In total, 27 articles ($n = 1,932$) were enrolled in this study. Vitamin D supplementation significantly improved fasting blood glucose, postprandial blood glucose, and quantitative insulin sensitivity check index in diabetes and prediabetes with baseline 25(OH)D<30 ng/ml. Higher percentages regressing from prediabetes to normal glucose status [1.60 (1.19, 2.17), $p = 0.002$, $n = 564$] and lower percentage progressing from prediabetes to diabetes [0.68 (0.36, 1.27), $p = 0.23$, $n = 569$] were found in the supplementation group. The positive effects of vitamin D supplementation on body mass index, waist, HDL-C, LDL-C, and CRP were also demonstrated. In conclusion, modest improvements in vitamin D supplementation on short-term glucose homeostasis, insulin sensitivity, and disease development in diabetes and prediabetes with 25(OH)D<30 ng/ml were demonstrated, but more research needs to be conducted in the future to support the clinical application. (Register ID: CRD42020186004)

Key Words: vitamin D, diabetes, prediabetes, glucose homeostasis, islet function

Mainly caused by islet β cell dysfunction and insulin resistance, diabetes is prevalent worldwide. Globally, more than 425 million people have diabetes, and more than \$727 billion have been spent on diabetes, of which more than 80% was devoted to its complications.⁽¹⁾ As the initial reversible stage of type 2 diabetes (T2D), prediabetes is considered as the “window of opportunity”. The prevalence in adults was reported as high as 35.7%.⁽²⁾ Even if sufficient lifestyle changes could slow the progression from prediabetes to diabetes, these are not enough and difficult to maintain.⁽³⁾ Thus, finding effective intervention methods to help slow or prevent the incidence and progression of prediabetes and diabetes is critical.

Vitamin D, a fat-soluble vitamin, plays important roles in not only bone growth and remodeling, but also common cancers, autoimmune diseases, cardiovascular disease, and so on. Many

observational studies found close associations between vitamin D status and the risk of T2D, and a meta-analysis enrolling 21 prospective studies showed a significantly inverse association between 25-dihydroxyvitamin D [25(OH)D] levels and the risk of T2D [0.62 (0.54–0.70)].⁽⁴⁾ Furthermore, basic experiments also provided theoretical support for the protective effects of vitamin D.⁽⁵⁾

However, the results of randomized controlled trials (RCTs) were obviously contradictory.^(3,6–8) By following up for an average of 2.5 years in 2,423 individuals at high risk of diabetes, the D2d study found that daily supplementation of 4,000 IU vitamin D₃ didn't significantly reduce the risk of diabetes.⁽³⁾ But the post hoc analysis found patients with baseline 25(OH)D<30 ng/ml showed greater supplementation benefits [0.38 (0.18, 0.80) vs 0.92 (0.78, 1.08)]. Moreover, one comment to this research emphasized that more studies should be conducted on individuals at earlier stages of T2D without obvious islet β cell dysfunction.⁽⁹⁾ Several prior systematic reviews were conducted and published 3 years ago to evaluate the effect of vitamin D supplementation in prediabetes and/or diabetes populations,^(10–12) but none initially aimed at vitamin D insufficient or deficient subjects.

Accordingly, we conducted a systematic review and meta-analysis of diabetes and prediabetes populations with baseline 25(OH)D<30 ng/ml to explore the effect of vitamin D supplementation on glucose homeostasis, islet function, disease development, and common metabolic indexes.

Materials and Methods

Literature retrieval. According to the PRISMA guidelines, we conducted this systematic review and meta-analysis and registered the pre-designed protocol at the PROSPERO website (ID: CRD42020186004). The electronic databases used in this study included Medline, Embase, Web of Science, and Cochrane Library. OpenGrey (<http://www.opengrey.eu/>) was used to research gray literature, and unpublished clinical trials were sought by www.controlled-trials.com. A historical search via references of relevant review articles was conducted as a supplement. The Medline search strategy is shown in Supplemental Fig. 1*. The main search terms for the other databases included

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*See online. <https://doi.org/10.3164/jcbrn.20-165>

doi: 10.3164/jcbrn.20-165
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(diabetes OR prediabetes) AND (vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol). All records were retrieved from the earliest available time to the end of May 2020, and no languages and regions were restricted.

Study selection. According to the diagnostic criteria of the 2011 American Endocrine Association, vitamin D insufficiency was defined as $20 \text{ ng/ml} \leq 25(\text{OH})\text{D} < 30 \text{ ng/ml}$, and vitamin D deficiency was defined as $25(\text{OH})\text{D} < 20 \text{ ng/ml}$. RCTs initially aiming at vitamin D insufficient or deficient diabetes or prediabetes including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) without severe complications were chosen. The intervention and control groups were either oral vitamin D supplementation vs placebo or vitamin D and calcium supplementation vs placebo and calcium supplementation.

Data extraction. The data extraction was initially conducted by one reviewer via a standardized Excel table and doubly checked by another reviewer. Basic characteristics including the first author, year of publication, and details of vitamin D supplementation were collected. Primary outcomes in this study were fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), postprandial blood glucose (PPBG), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI). HOMA-IR was defined as $\text{FBG (mM)} \times \text{fasting insulin (mIU/L)} / 22.5$, and QUICKI was $1 / (\text{FBG (mg/dl)} + \text{fasting insulin (mIU/L)})$, which separately implies insulin resistance and sensitivity. Secondary outcomes included weight, body mass index (BMI), waist, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and C-reactive protein (CRP). Average and SD of them between baseline and endpoints were extracted or calculated based on the Cochrane guidelines. The numbers progressing from prediabetes to diabetes and regressing from prediabetes to normal glucose status were extracted to calculate the risk ratio (RR). When important results could not be extracted or calculated, we contacted the corresponding authors to request more detailed information.

Ethics. This study was approved by the Ethics Committee of Peking Union Medical College, and in accordance with the current revision of the Helsinki Declaration. Because this study was a systematic review, no formed signed consent was needed.

Statistical analysis. Excel 2010 (Microsoft Inc., Redmond, WA), SPSS 22.0 software (IBM Inc., Armonk, NY), Review Manager Software 5.3 (Cochrane Collaboration), and GraphPad Prism (GraphPad Software, San Diego, CA) were used for analysis. The study quality and risk of bias were evaluated by two reviewers using latest revised Cochrane risk-of-bias tool for randomized trials (RoB 2), which consists of five domains, and the overall risk of bias generally corresponded to the worst risk of bias in any of the domains. Publication bias was assessed by visual inspection of funnel plots of primary outcomes.

Forest plots were produced to show the effect of vitamin D supplementation on primary outcomes. The random-effects model and inverse variance-weighted method were chosen. For continuous variables, the effect size was shown as mean change (MD) with 95% confidence interval (CI). For dichotomous outcomes, RR values with 95% CI were calculated with the Mantel-Haenszel method. The I^2 statistic was calculated to evaluate the heterogeneity among studies, and $I^2 \geq 50\%$ was considered high heterogeneity. When the two-sided p value was < 0.05 , the result was considered statistically significant.

The sensitivity analysis was conducted by excluding studies with high risk of bias, vitamin D supplementation in a single dose, or baseline mean $25(\text{OH})\text{D} > 20 \text{ ng/ml}$. The subgroup analysis was conducted based on the supplemental dose ($< 30,000 \text{ IU/week}$ vs $\geq 30,000 \text{ IU/week}$) and follow-up duration (< 4 months vs ≥ 4 months for diabetes group, < 6 months vs ≥ 6 months for

prediabetes group). Furthermore, trial sequential analysis (TSA) was conducted for primary outcomes in this study, and the MD and variance for the calculation of information sizes were 7.1 mg/dl and 10.7 mg/dl for FBG, 0.4% and 0.8% for HbA1c, 10.8 mg/dl and 16.0 mg/dl for PPBG, 14.6 pM and 37.4 pM for fasting insulin, 1.1 and 1.4 for HOMA-IR, and 0.1 and 0.015 for QUICKI, based on clinical experience and previous studies.^(7,13,14)

Results

Search results and quality evaluation. In total, 524 of 530 records were retrieved from electronic databases and other 6 records were recognized via other websites and the historical search. According to our eligibility criteria, 27 articles were eventually included in the systematic review (Fig. 1). The Sadiya team published 2 articles separately in 2015 and 2016, and the Tabesh team published 3 articles in 2015 and 2016. Thus, a total of 24 studies were eventually enrolled in the meta-analysis, of which 15 ($n = 1,101$) aimed at diabetes patients, and 9 ($n = 831$) aimed at prediabetes. Although we tried our best to contact the authors, we still could not retrieve the details of FPG, HbA1c, and fasting insulin from Tabesh's 2014 study. Since the methodological quality of the RCTs was variable, the revised RoB 2 tool was used to assess the study quality and risk of bias (Table 1). Of all 24 studies, 9 were considered high risk, 5 had some concerns, and 10 were deemed low risk.

Basic characteristics of enrolled studies. The basic characteristics of 24 studies are shown in Table 2, and some other characteristics are shown in Supplemental Table 1*. Since the patients in Tabesh's 2014 study were randomly assigned into 4 groups with/without calcium supplementation, we divided them into two study groups: (1) vitamin D supplementation vs placebo group and (2) vitamin D and calcium supplementation vs placebo and calcium supplementation. Respectively, the weighted average values of age, BMI, and baseline $25(\text{OH})\text{D}$ were 54.4 years of age, 28.9 kg/m^2 , and 15.4 ng/ml in diabetes, and 52.2 years of age, 31.1 kg/m^2 , and 12.2 ng/ml in prediabetes. The median supplemental dose and estimated time was $46,000 \text{ IU/week}$ and 15 weeks in diabetes, and $50,000 \text{ IU/week}$ and 26 weeks in prediabetes. At the endpoint, the levels of $25(\text{OH})\text{D}$ increased more obviously in the intervention groups than in the control groups [18.38 ($15.06, 21.69$)]. Accordingly, the concentration of parathyroid hormone (PTH) significantly decreased in the intervention groups [-7.71 ($-11.26, -4.16$)].

Glycose homeostasis. FBG ($n = 1,177$), HbA1c ($n = 1,354$), and PPBG ($n = 594$) were used to evaluate the effect on glycose homeostasis (Fig. 2). For FBG, there was a small but significant reduction in the intervention groups compared with the control groups in both diabetes and prediabetes individuals (all $p < 0.05$), but no significant difference in HbA1c. Since the high heterogeneity ($I^2 = 92\%$) in the diabetes groups was mainly caused by Khan's 2018 study, we excluded this study and found no protective effect of vitamin D supplementation [0.00 ($0.00, 0.01$)]. For PPBG, there was significant difference between the intervention and control groups in diabetes, but not in prediabetes with low heterogeneity. Furthermore, there was a significantly higher percentage in intervention groups regressing from prediabetes to normal glucose status [1.60 ($1.19, 2.17$), $p = 0.002$, $n = 564$], and lower percentage progressing from prediabetes to diabetes [0.68 ($0.36, 1.27$), $p = 0.23$, $n = 569$] with low heterogeneity ($I^2 = 0\%$ and 24% , respectively).

When excluding studies with high bias risk, the articles and sample sizes decreased considerably, and the significant outcomes turned negative. Excluding studies with vitamin D supplementation in a single dose didn't obviously change the results. The MD in studies with baseline mean $25(\text{OH})\text{D}$ levels $< 20 \text{ ng/ml}$ was more significant than in whole studies for PBG in both diabetes [-9.38 ($-20.12, 1.35$) vs -8.74 (-17.00 ,

Fig. 1. Flow chart of study retrieval and selection.

Table 1. The risk of bias and quality evaluation

Studies	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Diabetes						
2019 Lo ⁽¹⁴⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2018 Upreti ⁽⁷⁾	Some concerns	Low risk	Some concerns	Low risk	Some concerns	High risk
2018 Riek ⁽¹⁵⁾	Low risk	Some concerns	Low risk	Low risk	Some concerns	High risk
2018 Khan ⁽¹⁶⁾	Some concerns	Some concerns	Low risk	Low risk	Some concerns	High risk
2017 Randhawa ⁽¹⁷⁾	High risk	Low risk	Low risk	Low risk	Some concerns	High risk
2017 Gulseth ⁽¹⁸⁾	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
2017 Agarwal ⁽¹⁹⁾	Some concerns	Some concerns	Low risk	Low risk	Some concerns	High risk
2017 Alireza ⁽¹³⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2015 Sadiya ^(20,21)	Low risk	Low risk	Some concerns	Low risk	Some concerns	High risk
2014 Tabesh ^(22,23)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2014 Kampmann ⁽²⁴⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2014 Ryu ^(25,26)	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
2014 Baziar ⁽²⁷⁾	Some concerns	Low risk	Low risk	Low risk	Some concerns	High risk
2013 Yiu ⁽²⁸⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2008 Sugden ⁽²⁹⁾	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Prediabetes						
2020 Bhatt ⁽³⁰⁾	Some concerns	High risk	Low risk	Low risk	Low risk	High risk
2019 Wallace ⁽³¹⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2019 Niroomand ⁽³²⁾	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
2017 Moreira ⁽³³⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2016 Wagner ⁽⁶⁾	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
2015 Barendolts ⁽³⁴⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2014 Dutta ⁽³⁵⁾	Some concerns	High risk	High risk	Low risk	Low risk	High risk
2014 Oosterwerff ⁽³⁶⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2013 Davidson ⁽³⁷⁾	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Domain 1: risk of bias arising from the randomization process, Domain 2: risk of bias due to deviations from the intended interventions, Domain 3: risk of bias due to missing outcome data, Domain 4: risk of bias in measurement of the outcome, Domain 5: risk of bias in selection of the reported result.

Table 2. The basic characteristics of the enrolled studies

Year, first author	Number		Region	Age (years)		Supplemental type, dose	Time (weeks)	Maintain dose	Time (weeks)	With calcium
	Intervene	Control		Intervene	Control					
Diabetes										
2019 Lo ⁽¹⁴⁾	3/11	4/12	USA	66.1 ± 2.2	56.1 ± 1.5	Vit D ₂ , 50,000 IU/week	8	50,000 IU/month	17	None
2018 Upreti ⁽⁷⁾	15/15	23/7	India	48.3 ± 9.8	49.9 ± 6.9	Vit D ₃ , 60,000 IU/week	6	60,000 IU/month	18	None
2018 Riek ⁽¹⁵⁾	3/8	10/5	USA	57.6 ± 1.9	57.4 ± 1.8	Vit D ₃ , 4,000 IU/day	17	None	—	1,000 mg/day
2018 Khan ⁽¹⁶⁾	70	70	Pakistan	54.8 ± 8.6	58.4 ± 8.0	Vit D ₃ , 50,000 IU/week	12	None	—	None
2017 Randhawa ⁽¹⁷⁾	21/36	26/31	Pakistan	43.3 ± 4.9	42.4 ± 4.6	Vit D, 200,000 IU/month	13	None	—	None
2017 Gulseth ⁽¹⁸⁾	28	25	Norway	55.5 ± 9.2	55.9 ± 9.2	Vit D ₃ , 400,000 IU	Single	200,000 IU	Single	250 mg
2017 Agarwal ⁽¹⁹⁾	15/15	15/15	India	57.1 ± 11.7	53.6 ± 10.0	Vit D ₃ , 60,000 IU/15 day	13	None	—	None
2017 Alireza ⁽¹³⁾	15/15	15/15	Iran	60.5 ± 8.6	63.0 ± 10.7	Vit D, 50,000 IU/2 week	26	None	—	None
2015 Sadiya ^(20,21)	43	39	UAE	49 ± 8	48 ± 8	Vit D ₃ , 6,000 IU/day	13	3,000 IU/day	13	None
2014 Tabesh ^(22,23)	15/14	14/16	Iran	50.2 ± 6.6	51.0 ± 6.1	Vit D ₃ , 50,000 IU/week	8	None	—	None
2014 Kampmann ⁽²⁴⁾	15/15	14/15	Iran	60.5 ± 8.6	63.0 ± 10.7	Vit D ₃ , 50,000 IU/week	8	None	—	1,000 mg/day
2014 Ryu ^(25,26)	7	8	Denmark	61.6 ± 4.4	57 ± 4.5	Vit D ₃ , 11,200 IU/day	2	5,600 IU/day	10	None
2014 Baziar ⁽²⁷⁾	64	65	Korea	54.8 ± 7.6	55.9 ± 8.1	Vit D ₃ , 2,000 IU/day	24	None	—	200 mg/day
2013 Yiu ⁽²⁸⁾	28/13	26/14	Iran	50.3 ± 6.7	52.8 ± 6.3	Vit D ₃ , 50,000 IU/day	8	None	—	None
2008 Sugden ⁽²⁹⁾	27/27	23/23	Finland	65.8 ± 7.3	64.9 ± 8.9	Vit D ₃ , 5,000 IU/day	12	None	—	None
2019 Lo ⁽¹⁴⁾	10/7	8/9	Scotland	64.9 ± 10.3	63.5 ± 9.5	Vit D ₂ , 100,000 IU	Single	None	Single	None
Prediabetes										
2020 Bhatt ⁽³⁰⁾	41	41	India	NA	NA	Vit D ₃ , 60,000 IU/week	8	200 IU/day	70	1 mg/day
2019 Wallace ⁽³¹⁾	34	30	UK	52.4 ± 2.0	54.0 ± 1.7	Vit D ₃ , 3,000 IU/day	26	None	—	None
2019 Niroomand ⁽³²⁾	43	40	Iran	45 ± 14	48 ± 11	Vit D ₃ , 50,000 IU/week	13	50,000 IU/month	13	None
2017 Moreira ⁽³³⁾	32	31	Canada	49.1 ± 13.9	49.1 ± 13.9	Vit D ₃ , 28,000/week	24	None	—	None
2016 Wagner ⁽⁶⁾	9/12	11/11	Sweden	67.6 ± 4.0	67.0 ± 2.8	Vit D ₃ , 30,000 IU/week	8	None	—	None
2015 Barengolts ⁽³⁴⁾	87	86	USA	58.2 ± 6.0	59.8 ± 6.0	Vit D ₂ , 50,000 IU/week	1 year	To 40–100 ng/ml	Every 3 month	None
2014 Dutta ⁽³⁵⁾	25/43	26/31	India	48.4 ± 10.5	47.4 ± 11.5	Vit D ₃ , 60,000 IU/week	>1year	None	—	500 mg/month
2014 Oosterwerff ⁽³⁶⁾	53	57	Holland	48.9 ± 10.3	51.5 ± 10.5	Vit D ₃ , 1,200 IU/day	16	None	—	500 mg/month
2013 Davidson ⁽³⁷⁾	15/38	20/36	USA	52.3 ± 8.0	52.5 ± 7.0	Vit D, to achieve 65–90 ng/ml	1 year	None	—	None

The number of study populations is shown as male/female or total.

−0.48)] and prediabetes groups [−2.72 (−4.63, −0.82) vs −2.20 (−3.90, −0.50)] and PPBG in prediabetes groups [−8.36 (−17.86, 1.15) vs −5.73 (−14.66, 3.20)]. By subgroup analysis, the effect size was found more significant in supplemental dose ≥30,000 IU/week groups than in <30,000 IU/week groups for FBG [−3.98 (−7.07, −0.89) vs −2.82 (−7.83, 2.18)] and HbA1c [−0.16 (−0.30, −0.03) vs −0.03 (−0.12, 0.07)] but no obvious change in PPBG, and more significant in follow-up duration ≥4/6 months groups than in <4/6 months groups for FBG [−3.50 (−6.74, −0.25) vs [−3.82 (−8.79, 1.15)] and PPBG [−18.32 (−36.13, −0.50) vs −8.04 (−30.53, 14.45)] but no obvious change in HbA1c. Based on the pre-set MD and variations, a TSA boundary was only drawn for HbA1c (Supplemental Fig. 2*). The negative conclusion could not be deemed true, with the present patients less than the required information size.

Islet function. The changes in fasting insulin ($n = 501$), HOMA-IR ($n = 826$), and QUICKI ($n = 282$) were used to evaluate the effect on insulin secretion, insulin resistance, and insulin sensitivity, respectively. As shown in Fig. 3, vitamin D supplementation significantly improved HOMA-IR and QUICKI in the diabetes groups and fasting insulin in the prediabetes groups. The high heterogeneity of fasting insulin in the diabetes groups was mainly caused by Kampmann's 2014 study. After excluding this study, significant differences between intervention and control groups were also found [−20.05 (−24.37, −15.73)].

After excluding studies with a high risk of bias, the difference in fasting insulin and HOMA-IR between intervention and control groups was no longer obvious. But excluding studies with vitamin D supplementation in a single dose didn't obviously affect the results. Excluding studies with baseline mean 25(OH)D levels >20 ng/ml almost didn't change the studies' numbers. The effect size was less significant in supplemental dose ≥30,000 IU/week groups than in <30,000 IU/week groups for fasting

insulin [0.00 (−26.43, 26.43) vs −18.73 (−29.40, −8.05)], while there was no significant change in HOMA-IR and QUICKI, and more obvious in follow-up duration ≥4/6 months groups than in <4/6 months groups [−17.48 (−25.78, −9.19) vs 6.53 (−32.26, 45.31)], but no obvious change in HOMA-IR and QUICKI. Based on the pre-set MD and variations, a TSA boundary was drawn for QUICKI, which implied the positive conclusion was likely to be true (Supplemental Fig. 2*).

Common metabolic indexes. The effects of vitamin D supplementation on common metabolic indexes were summed up in Table 3. Since the basic characteristics of enrolled population, supplemental dose, and follow-up duration largely varied, the heterogeneities were generally high for most indexes. With all $p < 0.05$, vitamin D supplementation significantly improved the situation of BMI, waist, HDL-C, LDL-C, and CRP in diabetes but not obviously in prediabetes.

After high-risk studies were excluded for sensitivity analysis, the difference of TC in diabetes became significant [−0.25 (−0.47, −0.02) vs −0.09 (−0.31, 0.14)], and the difference in other indexes didn't obviously change. The improvement was more significant in vitamin D supplemental dose >30,000 IU/w for BMI [−0.14 (−0.23, −0.06) vs 0.02 (−0.23, 0.26)] and LDL-C [−0.20 (−0.25, −0.14) vs −0.06 (−0.24, 0.11)], but less significant for TG [−0.09 (−0.27, 0.09) vs −0.15 (−0.26, −0.03)], and didn't change considerably in the other indexes, of which some were not suitable for the subgroup analysis due to the lack of studies. Moreover, the difference was more significant in follow-up duration ≥4/6 months group for HDL-C [0.08 (0.04, 0.12) vs 0.04 (−0.01, 0.10)] and TG [−0.16 (−0.24, −0.08) vs −0.04 (−0.29, 0.21)], but less significant for BMI [−0.02 (−0.27, 0.22) vs −0.14 (−0.23, −0.05)], waist, [−0.41 (−0.70, −0.13) vs −0.63 (−3.60, 2.34)], TC [−0.02 (−0.27, 0.22) vs −0.14 (−0.23, −0.05)], and CRP [0.03 (−0.85, 0.92) vs −0.52 (−0.85, −0.18)], and not

*See online. <https://doi.org/10.3164/jcfn.20-165>

Fig. 2. Forest plots of glucose homeostasis. (A) FBG (mg/dl), (B) HbA1c (%), and (C) PPBG (mg/dl).

Fig. 3. Forest plots of islet function. (A) Fasting insulin (pmol/L), (B) HOMA-IR, and (C) QUICKI.

Table 3. The effect size of vitamin D supplementation on other metabolic measurements

	Diabetes				Prediabetes				Total			
	<i>n</i>	Difference	<i>p</i>	<i>I</i> ²	<i>n</i>	Difference	<i>p</i>	<i>I</i> ²	<i>n</i>	Difference	<i>p</i>	<i>I</i> ²
Weight (kg)	320	-0.04 (-0.29, 0.21)	0.78	69%	165	-1.11 (-5.49, 3.28)	0.62	0%	485	-0.04 (-0.27, 0.19)	0.76	55%
BMI (kg/m ²)	503	-0.13 (-0.22, -0.04)	0.005	64%	376	-0.14 (-0.41, 0.13)	0.31	0%	879	-0.12 (-0.20, -0.05)	0.001	41%
Waist (cm)	200	-0.44 (-0.71, -0.16)	0.002	52%	208	-0.08 (-1.17, 1.00)	0.88	0%	408	-0.43 (-0.59, -0.28)	<0.001	0%
SBP (mmHg)	408	-2.30 (-7.53, 2.94)	0.39	79%	83	2.00 (-4.14, 8.14)	0.52	—	491	-1.75 (-6.37, 2.88)	0.46	76%
DBP (mmHg)	374	-0.63 (-2.66, 1.41)	0.54	54%	83	-1.00 (-4.91, 2.91)	0.62	—	457	-0.67 (-2.41, 1.07)	0.45	45%
TC (mM)	460	-0.09 (-0.31, 0.14)	0.45	94%	125	-0.05 (-0.78, 0.67)	0.89	86%	585	-0.07 (-0.28, 0.13)	0.48	93%
HDL-C (mM)	460	0.06 (0.01, 0.10)	0.01	90%	229	0.07 (-0.01, 0.14)	0.11	0%	689	0.06 (0.02, 0.10)	0.006	86%
LDL-C (mM)	322	-0.22 (-0.25, -0.18)	<0.001	0%	229	-0.08 (-0.17, 0.02)	0.13	0%	551	-0.18 (-0.24, -0.13)	<0.001	37%
TG (mM)	445	-0.17 (-0.33, -0.00)	0.05	94%	229	0.03 (-0.27, 0.34)	0.83	78%	674	-0.11 (-0.26, 0.03)	0.13	92%
CRP (mg/L)	314	-0.53 (-0.85, -0.21)	0.001	60%	104	0.09 (-0.81, 0.99)	0.84	—	418	-0.46 (-0.78, -0.15)	0.004	59%

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; PTH, parathyroid hormone; CRP, C-reactive protein.

obvious in the other indexes.

Publication bias. According to the recommendations in the Cochrane guidelines, statistical tests for the asymmetry of funnel plots should be conducted only when the studies included in meta-analyses ≥ 10 . Thus, we only presented the visual funnel plots in Supplemental Fig. 3*, which were generally symmetrical except for PPBG and HOMA-IR. The bias in HbA1c and fasting insulin was mainly caused by Khan's 2018 and Kampmann's 2014 studies, respectively. But excluding them didn't obviously affect the results. Since there was no significant effect of vitamin D supplementation on HbA1c and fasting insulin, the existing publication bias would not have an obvious impact on the interpretation of the results.

Discussion

A systematic review and meta-analysis including 24 RCTs ($n = 1,932$) was conducted in this study. We found vitamin D supplementation significantly improved FBG, PPBG, HOMA-IR, and QUICKI in diabetes, and PBG and PPBG and fasting insulin in prediabetes, with baseline 25(OH)D levels <30 ng/ml. Moreover, the percentage regressing from prediabetes to normal glucose status was significantly higher in the intervention group, and progressing from prediabetes to diabetes was lower. The positive effects on BMI, waist, HDL-C, LDL-C, and CRP were also demonstrated in this study.

With the decrease in PTH, 25(OH)D increased more obviously in the intervention groups than in the control groups [18.38 (15.06, 21.69)]. Although 18 studies ($n = 1,354$) were included to evaluate the effect of vitamin D supplementation on HbA1c, no significant difference was found, which was consistent with previous meta-analyses.^(10,12) But the TSA analysis implied that the negative result of HbA1c still needs to be verified by including more studies. Different from previous reports,^(10,11) significantly positive effects on FBG and PPBG were demonstrated, which were more significant in higher supplemental dose, longer follow-up duration, and lower 25(OH)D level groups. The positive effects of vitamin D supplementation were found for fasting insulin and QUICKI, and that of QUICKI was considered as true positive by TSA analysis. Moreover, the results showed that vitamin D supplementation had good effect on HOMA-IR in diabetes, but bad for prediabetes, which were contradictory across several systematic reviews.^(10,12) But the sensitivity analysis showed that many significant outcomes turned negative after excluding studies with a high risk of bias, which was partly caused by the obvious decrease in the study numbers.

Of note, most individuals enrolled in this study were obese

(weighted average BMI: 29.8 kg/m²). As a fat-soluble substance, vitamin D is preferentially deposited in body fat, so the bioavailability of vitamin D supplementation in obese individuals will decrease,⁽³⁸⁾ which could negate the potential effect of vitamin D supplementation. Moreover, the averages of 25(OH)D at the endpoints in the intervention groups in at least 6 studies didn't reach 30 ng/ml, which meant that many individuals were still vitamin D insufficient or even deficient after supplementation. The median follow-up time was 15 weeks in the diabetes groups and 26 weeks in the prediabetes groups, which meant that the power to recognize differences in long-term monitoring indexes such as HbA1c was low. This could also partly explain why the difference in HbA1c in diabetes was less obvious than in prediabetes. Different measurement methods of 1,25-dihydroxyvitamin D [1,25(OH)₂D] across studies could also have influenced the study results. Moreover, "free hormone hypothesis" demonstrated that only free 25(OH)D could be transformed into active 1,25(OH)₂D by 1- α hydroxylase in cells and produced biological effects, which demonstrated that free 25(OH)D could better evaluate human vitamin D status.⁽³⁹⁾ However, none of the studies measured the levels of free 25(OH)D, which need to be confirmed in future studies. Furthermore, the contradictions between the RCTs and observational studies implied that the causal association between vitamin D and some diseases including glucose metabolism remained unclear. The lower levels of 25(OH)D could have been partly induced by the status of diseases with fewer outdoor activities. Moreover, a recent study⁽⁴⁰⁾ found that the plasma 1,25(OH)₂D levels decreased in streptozotocin-induced diabetes rats, in which high Cyp24a1 expression levels may play an important role.

There are some strengths in our study. Based on the results of previous studies,^(8,9,13) we found negative conclusions were more likely in studies enrolling patients with higher baseline 25(OH)D levels. Thus, we only included patients with baseline 25(OH)D <30 ng/ml. To the best of our knowledge, this was the first meta-analysis initially aimed at insufficient or deficient diabetes and prediabetes subjects instead of simple subgroup analysis. With 62.1% articles published in the last five years, our study could also update previous results of meta-analysis. In addition, 28 of 29 articles were published after 2010, when the automation of measurement methods for 25(OH)D had greatly developed, which made the measurements more comparable, however, the consistency between different platforms was still not satisfying.⁽⁴¹⁾ Furthermore, we enrolled both diabetes and prediabetes patients, and comprehensively analyzed the effect of vitamin D supplementation on glycose homeostasis, islet function, disease development, and common metabolic indexes. Since calcium can suppress 1,25(OH)₂D and was independently

*See online. <https://doi.org/10.3164/jcfn.20-165>

associated with glucose handling and insulin secretion, only the type of vitamin D supplementation vs placebo or vitamin D and calcium supplementation vs placebo and calcium supplementation were enrolled in this study to offset the potential effect caused by calcium supplementation. We also only enrolled studies with oral supplementation to reduce heterogeneity and interference.

This study had limitations that merit mention. Although we searched various databases and websites, it is possible that some articles and trials were missed, and we could not contact one study's corresponding author. Moreover, the studies enrolled in this meta-analysis had small simple sizes and variable study quality. We enrolled both diabetes and prediabetes including IGT and IFG subjects in this study; however, the diagnostic criteria differed and were unclear in some studies. Furthermore, IGT was more sensitive than IFG for predicting progression to diabetes, and disease severity and duration were also different across the studies. Although most of the studies used vitamin D₃ as the type of supplement, several used vitamin D₂ or didn't clearly report the type, and the vitamin D supplemental doses and follow-up durations largely varied. Also, many studies didn't report diabetes medication usage, dietary intake, extra supplementation, or sun exposure, which could affect human vitamin D status.

In conclusion, the meta-analysis based on current RCTs showed modest improvements of vitamin D supplementation on short-term glycose homeostasis, insulin sensitivity, and disease development in diabetes and prediabetes with 25(OH)D<30 ng/ml, but the evidence to supporting clinical application remained insufficient. More high-quality RCTs with longer follow-up durations in larger populations especially vitamin D deficient individuals need to be conducted. The optimal supplemental dose, appropriate human vitamin D status, and more accurate standardized detection methods for 25(OH)D should be explored and recommended in the future.

Acknowledgments

I'd like to express my sincere appreciation to my partner, Bo

Guo, and my supervisor, Ling Qiu and Songlin Yu, for their academic help and guidance of this article.

This work was funded by research grants from the National Natural Science Foundation of China (grant number: 81702060) and China Capital Health Research and Development of Special Project (grant number: 2020-1-4014). This work is also supported by Beijing Key Clinical Specialty for Laboratory Medicine-Excellent Project (No. ZK201000).

Abbreviations

BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
DBP	diastolic blood pressure
FBG	fasting blood glucose
HbA1c	glycosylated hemoglobin
HDL-C	high density lipoprotein cholesterol
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LDL-C	low density lipoprotein cholesterol
MD	mean change
1,25(OH) ₂ D	1,25-dihydroxyvitamin D
25(OH)D	25-dihydroxyvitamin D
PPBG	postprandial blood glucose
PTH	parathyroid hormone
QUICKI	quantitative insulin sensitivity check index
RCT	randomized controlled trial
RR	risk ratio
SBP	systolic blood pressure
TC	total cholesterol
TG	triglyceride
TSA	trial sequential analysis
T2D	type 2 diabetes

Conflict of Interest

No potential conflicts of interest were disclosed.

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