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Research Article

Effects of Vitamin D Supplementation on Renal Function, Inflammation and Glycemic Control in Patients with Diabetic Nephropathy: a Systematic Review and Meta-Analysis

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Key Words
Vitamin D • Diabetic nephropathy • Randomized controlled trials • Meta-analysis

Abstract
Background/Aims: Vitamin D (VD) is widely recognized as renal protective. However, whether VD supplementation provides benefit to patients with diabetic nephropathy (DN) remains controversial. Here, we performed a meta-analysis to systematically evaluate the impact of VD supplementation on indexes of renal function, inflammation and glycemic control in DN patients, and to explore the potential renal protective mechanism of VD. ***Methods:*** We searched Pubmed, Embase, Cochrane Library, and three major Chinese biomedical databases (CNKI, WANGFANG and VIP) for randomized controlled trials (RCTs) examining the effects of VD or its analogs in DN patients, published between September 2007 and July 2018. Quality assessment and data extraction were performed independently by two authors, according to the Cochrane systematic review methods. Meta-analysis based on the extracted results were performed via Revman 5.2 software. ***Results:*** We included 20 RCTs representing 1,464 patients with DN in this meta-analysis. VD supplementation significantly reduced 24-hour urine protein [MD = -0.26; 95% CI (-0.34, -0.17); $P < 0.00001$; $I^2 = 95\%$], UAER [MD = -67.36; 95% CI (-91.96, -42.76); $P < 0.00001$; $I^2 = 97\%$], hs-CRP [MD = -0.69; 95% CI (-0.86,-0.53); $P < 0.00001$; $I^2 = 0\%$], TNF-α [MD = -56.79; 95% CI (-77.05, -36.52); $P < 0.00001$; $I^2 = 89\%$] and IL-6 [MD = -0.73; 95% CI(-1.03, -0.44); $P < 0.00001$; $I^2 = 0\%$]. However, VD supplementation failed to decrease SCr [MD = -0.83; 95% CI (-3.67,2.02); $P = 0.57$; $I^2 = 0\%$] or increase eGFR [MD = 2.13; 95% CI (-2.06, 6.32); $P = 0.32$; $I^2 = 0\%$]. In addition, VD supplementation showed no impact on indexes of glycemic control, such as HbA1c [MD = 0.01; 95% CI (-0.09, 0.11); $P = 0.84$; $I^2 = 0\%$] and FBG [MD = -0.05; 95% CI (-0.29, 0.20); $P = 0.70$; $I^2 = 0\%$]. Analysis of 24-hour urine protein, SCr, eGFR, hs-CRP or HbA1c revealed no difference between subgroups based

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on the type of VD supplementation, including calcitriol, alfacalcidol and vitamin D3, and the dose or duration of calcitriol usage. ***Conclusion:*** In patients with DN, VD supplementation provides beneficial effects on 24-hour urine protein and inflammation indexes, but not on SCr, eGFR or glycemic control indexes. More RCTs that comprehensively evaluate the impact of VD supplementation on indexes of renal function, inflammation and glycemic control in DN patients are required in order to reach conclusive results.

Introduction

Diabetic Nephropathy (DN) is one of the most common microvascular complications of diabetes and the major cause of end stage renal disease (ESRD) [1]. Diabetes is likely to remain a huge threat to public health in the 21st century [2]. According to the Diabetic Charter for Canada [3], the prevalence of diabetes in Canada is 9.2% in 2016, resulting a $3.4 billion economic cost; Such cost is estimated to reach $5 billion with 11.6% of diabetic prevalent rate in 2026. In the U.S., the total estimated cost of diagnosed diabetes in 2017 is $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity [4]. The rising prevalence of diabetes and the high cost of ESRD treatment have brought heavy financial burden to the healthcare systems worldwide. Therefore, it is urgent to explore low-cost and effective treatment plans in order to decrease the incidence and mortality rate of DN.

Generally, Vitamin D (VD), a fat-soluble vitamin formed from 7-dehydrocholesterol in the skin, is transported to the liver and hydroxylated to $25(OH)D_3$, which is then transported to the kidney and further hydroxylated to 1, $25(OH)D_3$. This active form of VD binds to vitamin D receptor (VDR) in target cells and plays a central role in calcium homeostasis [5]. Importantly, many studies have shown that VD plays a renal protective role [6, 7]. VD supplementation is then expected to delay the progression of DN. Nonetheless, it remains controversial whether VD supplementation provides clinical benefit to DN patients. One previous meta-analysis showed that Vitamin D3 ameliorates proteinuria and protects DN patients from kidney injury [8]. However, other meta-analysis did not find potential benefit of vitamin D supplementation on UACR [9]. Therefore, we sought to perform a systematic review of randomized controlled trials (RCTs) to evaluate the effects of VD and its analogs on indexes of renal function, inflammation and glycemic control in DN patients, and to explore the potential renal protective mechanism of VD in DN.

Materials and Methods

Literature search strategy

We performed a systematic literature search (Pubmed, Embase, Cochrane Library, CNKI, WANGFANG and VIP) to identify articles published between September 2007 and July 2018, using the search items *vitamin D, cholecalciferol, calcitriol, 1, 25(OH)D_3, paricalcitol* and *diabetic nephropathy* in the title, abstract, and keywords with no restriction imposed. Additional papers were found through a manual search of reference lists of review articles. The literature search was conducted by two of the authors (Y.W. and S.Y.) independently.

Selection criteria

We included RCTs that assessed the impact of VD or its analogs on DN, regardless of whether blinding was used in the trials, in the following groups: treatment group that received supplementation of VD or its analogs *vs.* control group that received placebo or blank treatment, or that received placebo/blank plus conventional treatment when it was used in both arms of study. All included study participants were diagnosed with diabetes according to the 1999 WHO diagnostic criteria for diabetes [10], and concomitantly diagnosed with diabetic nephropathy based on the Mogensen classification of diabetic nephropathy [11].

Exclusion criteria

Exclusion criteria were: 1. RCTs that were missing important and unrecoverable information; 2. Duplicate publications; 3. Reviews, animal studies or case reports; 4. RCTs with unclear primary outcome or outcome measures; 5. RCTs based on non-DN patients; 6. Sample size of either experimental group or control group was less than 20; 7. RCTs whose data were not described with mean and standard deviation.

Primary outcome measures

Primary outcome measures included: 24-hour urine protein; urinary albumin excretion rate (UAER); serum creatinine (SCr); estimated glomerular filtration rate (eGFR); high-sensitivity C-reactive protein (hs-CRP); tumor necrosis factor-alpha (TNF-α); interleukin 6 (IL-6); hemoglobin A1c (HbA1c); fasting blood glucose (FBG).

Quality assessment

The quality assessment of the selected RCTs was performed independently by two authors (Y.W. and S.Y.). If there were any discrepancies of whether a specific RCT should be included, the last author (Y.B.) was consulted to reach consensus. Based on the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.2.0), all included RCTs were assessed according to the following criteria: 1) Was randomization properly used? 2) Was there allocation concealment? 3) Were methods of blinding used? 4) Was there incomplete-data bias? 5) Was there selection bias? 6) Were there other potential biases?

Data synthesis and statistical analysis

The results of all 20 included RCTs were pooled and analyzed via Revman Review Manager 5.2. All continuous variables were expressed as mean deviation (MD) and standard deviation (SD) with 95% confidence interval (CI). The χ^2 test was used for heterogeneity assessment. In the absence of clinical heterogeneity ($P \geq 0.05$ and $I^2 \leq 50\%$), the fixed effect model of meta-analysis was applied; in the presence of substantial heterogeneity between studies ($P < 0.05$ and $I^2 > 50\%$), the sensitive analysis was performed to find out the source of heterogeneity and to assess whether the results could be significantly influenced; if the source of heterogeneity remained unclear, the random effect model of meta-analysis was used. A P value of <0.05 was considered statistically significant.

Results

Summary of literature search and study selection

We identified 1,152 articles via literature search. 42 studies remained after reviewing title and abstract, and excluding non-RCTs, duplicate publications and nonclinical research. We further examined the full text of these 42 studies and excluded those that enrolled less than 20 cases for either treatment or control group, or failed to provide qualified endpoints or complete data for our meta-analysis. Ultimately 20 RCTs [12-31] were included in the review (6 published in English and 14 in Chinese), involving a total of 1, 464 participants (T/C: 732/732) (Fig. 1). The characteristics of all included RCTs were summarized in Table 1 and the methodological quality of the included RCTs were shown in Fig. 2.

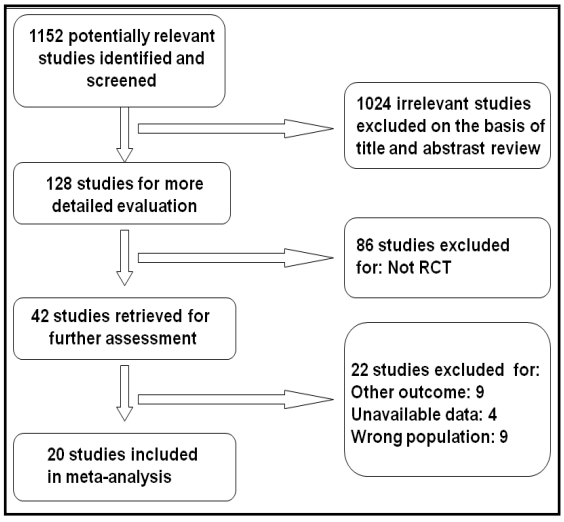

Fig. 1. Diagram of study selection.

Table 1. Characteristics of 20 included RCTs. Abbreviations: T: treatment group; C: control group

Author and Year	Country	Study Population	Participants (T/C)	Age (y)	Treatment (T)	Treatment (C)	Study Duration
Xu 2011	China	T2DN	35/35	T: 51.2±13.1 C: 50.4±12.3	Alfacalcidol 0.5 μg/day	w/o alfacalcidol	12 weeks
Ding 2011	China	T1DN+T2DN	24/22	T: 53.0±7.9 C: 51.0±8.5	Calcitriol 0.5 μg/day	w/o calcitriol	6 months
Zhou 2012	China	T1DN+T2DN	20/20	T: 49.8±13.2 C: 49.8±13.2	Alfacalcidol 0.25 μg/day + Telmisartan 20-40 mg/day	Telmisartan 20-40 mg/day	12 weeks
Huang 2012	China	T2DN	22/24	T: 61.1±10.4 C: 60.0±12.2	Cholecalciferol 800 IU/Day	w/o cholecalciferol	6 months
Krairittichai 2012	Thailand	T2DN	46/45	T: 59.7±8.5 C: 61.8±11.9	Calcitriol 0.5 ug twice weekly	w/o calcitriol	16 weeks
Ahmadi 2012	Iran	T2DN	30/30	T: 58.3±11.1 C: 57.1±10.7	Vitamin D3 pearl 50,000 IU/week	Placebo	12 weeks
Guan 2012	China	T1DN+T2DN	33/32	T: 53.5±8.4 C: 54.3±8.3	Calcitriol 0.25 μg/day (increased to 0.5 μg/day after 1 week) + Telmisartan 40 mg/day (increased to 80 mg/day after 2 weeks)	Telmisartan 40 mg/day (increased to 80 mg/day after 2 weeks)	6 months
Zhou 2013	China	T1DN+T2DN	36/36	T: 47.7±11.4 C: 43.6±9.4	Calcitriol 0.25 μg/day (increased to 0.5 μg/day after 1 week) + Irbesartan 150 mg/day (increased to 300 mg /day after 2 weeks)	Irbesartan 150 mg/day (increased to 300 mg /day after 2 weeks)	6 months
Zhen 2013	China	T1DN+T2DN	34/34	T: 53.1±8.0 C: 52.4±8.1	Calcitriol 0.25 μg/day (increased by 0.25 μg/day every 4 weeks to a maximum dose of 0.5-1.0 μg/day)	w/o calcitriol	6 months
Mustafar 2014	Malaysia	T1DN+T2DN	25/25	T: 55.0±9.5 C: 52.0±20.5	Calcitriol 0.5 μg + Calcium carbonate 500 mg/Day	Calcium carbonate 500 mg/Day	12 weeks
Duan 2014	China	T1DN+T2DN	45/45	T: 56.0±6.1	Calcitriol 0.25 μg/day	w/o calcitriol	3 months
Chen 2014	China	T1DN+T2DN	43/43	T: 57.3±6.1	Calcitriol 0.25 μg/day (increased to 0.5 μg/day after 1 week) + Telmisartan 40 mg/day (increased to 80 mg/day after 2 weeks)	Telmisartan 40 mg/day (increased to 80 mg/day after 2 weeks)	6 months
Wang 2014	China	T2DN	21/24	T: 53.0±6.5 C: 51.0±7.5	Alfacalcidol 0.25 μg/day + Irbesartan 150-300 mg/day	Irbesartan 150-300 mg/day	12 weeks
Wang 2016	China	T1DN+T2DN	43/41	T: 50.5±6.2 C: 49.7±6.0	Calcitriol 0.25 μg/day (increased to 0.5 μg/day after 1 week) + Telmisartan 40 mg/day (increased to 80 mg/day after 2 weeks)	Telmisartan 40 mg/day (increasing to 80 mg/day after 2 weeks)	6 months
Wang 2016	China	T2DN	68/68	T: 56.6±3.2	Calcitriol 0.25 μg/day	Placebo	24 weeks
Liu 2016	China	T1DN+T2DN	60/60	T: 51.2±5.9 C: 51.2±6.0	Calcitriol 0.25 μg/day + Losartan Potassium 25-50 mg/day	Losartan Potassium 25-50 mg/day	3 months
Tiryaki 2016	Turkey	T2DN	48/50	T: 49.6±16.6 C: 52.4±18.6	Calcitriol 0.25 μg/day	Placebo	24 weeks
Li 2016	China	T1DN+T2DN	40/40	T: 57.6±9.4 C: 57.8±9.0	Calcitriol 0.25 μg/day	w/o calcitriol	12 weeks
He 2017	China	T1DN+T2DN	30/30	T: 50.0±9.6 C: 50.0±9.5	Calcitriol 0.25 μg/day + Valsartan 80-160 mg/day	Valsartan 80-160 mg/day	6 months
Momeni 2017	Iran	T2DN	29/28	T: 62.9±9.3 C: 62.4±9	Vitamin D3 pearl 50,000 IU/week	Placebo	8 weeks

The impact of VD supplementation on indexes of renal function

24-hour urine protein. Eleven RCTs involving 816 participants (T/C: 409/407) reported sufficient data for inclusion in the meta-analysis to measure the effect of VD on 24-hour urine protein (Fig. 3A-C). VD supplementation significantly decreased 24-hour urine protein by 0.26 g [MD = -0.26; 95% CI (-0.34, -0.17); $P < 0.00001$] relative to control with high level of heterogeneity between studies [$I^2 = 95\%$] in DN patients. Analysis based on type of VD supplementation indicated significant decrease of 24-hour urine protein in patients assigned to receive calcitriol [MD = -0.25; 95% CI (-0.34, -0.16); $P < 0.00001$], alfacalcidol [MD = -0.44; 95% CI (-0.85, -0.03); $P = 0.04$], or vitamin D3 [MD = -0.29; 95% CI (-0.54, -0.04); $P = 0.03$] relative to their control treatments (Fig. 3A). Further subgroup analyses based on either dose (Fig. 3B) or duration of calcitriol intervention (Fig. 3C) demonstrated that: 24-hour urine protein was reduced in response to VD at lower dose of calcitriol (≤ 0.25 μg/d) [MD = -0.19; 95% CI (-0.36, -0.01); $P = 0.04$] with high study heterogeneity [$I^2 = 73\%$; $P = 0.02$]; at higher dose of calcitriol (≥ 0.25 μg/d) [MD = -0.31; 95% CI (-0.44, -0.19); $P < 0.00001$] with low study heterogeneity [$I^2 = 46\%$; $P = 0.10$]; at shorter duration of calcitriol usage (2-3 months) [MD = -0.19;

95% CI (-0.36, -0.01), P = 0.04] with high study heterogeneity [I^2 = 73%; P = 0.02]; and at longer duration of calcitriol usage (4-6 months) [MD = -0.31; 95% CI (-0.44, -0.19); P < 0.00001] with low study heterogeneity [I^2 = 46%; P = 0.10].

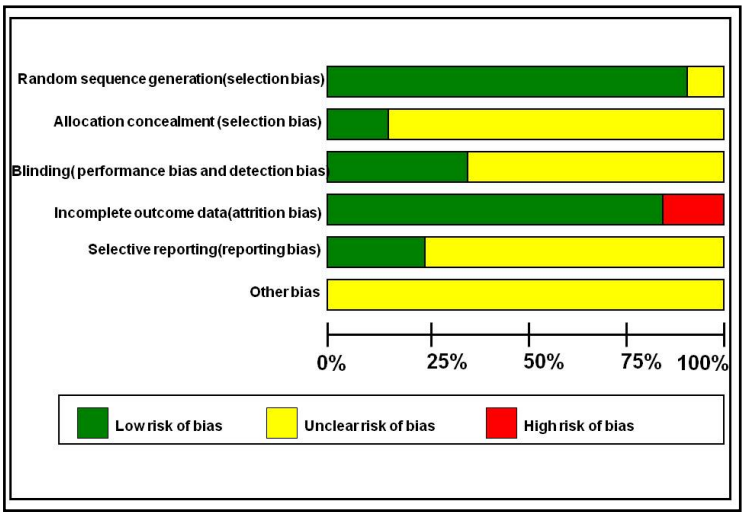

Fig. 2. Methodological quality of the included studies.

UAER. The effect of VD supplementation on UAER was evaluated in eight RCTs involving 676 participants (T/C: 339/337) (Fig. 4A-C). UAER was markedly decreased in DN patients in response to VD [MD = -67.36; 95% CI (-91.96, -42.76); P < 0.00001] with high level of heterogeneity between studies [I^2 = 97%; P < 0.00001]. Analysis based on type of VD supplementation showed significant decreases of UAER in patients assigned to receive calcitriol [MD = -77.80; 95% CI (-110.21, -45.38); P < 0.00001], or alfacalcidol [MD = -44.26; 95% CI (-54.74, -33.78); P < 0.00001] relative to their control treatments (Fig. 4A). Subgroup analyses based on either dose (Fig. 4B) or duration of calcitriol usage (Fig. 4C) showed that calcitriol reduced UAER at lower dose (≤ 0.25 μg/d) [MD = -87.07; 95% CI (-137.21, -36.93); P = 0.0007] with high study heterogeneity [I^2 = 98%; P< 0.00001]; at higher dose (>0.25 μg/d) [MD = -65.06; 95% CI (-109.54, -20.58); P = 0.004] with high study heterogeneity [I^2 = 86%; P = 0.008]; at shorter duration (2-3 months) [MD = -30.11; 95% CI (-60.17, -0.05); P =0.05] with high study heterogeneity [I^2 = 94%; P < 0.0001]; and at longer duration (4-6 months) [MD = -109.01; 95% CI (-171.65, -46.37); P = 0.0006] with high study heterogeneity [I^2 = 98%; P < 0.00001].

SCr. Nine RCTs involving 560 participants (T/C: 283/277) reported SCr as primary or secondary outcome measure (Fig. 5A-C). VD supplementation showed no impact on SCr in DN patients [MD = -0.83; 95% CI (-3.67, 2.02); P = 0.57] with low level of heterogeneity between studies [I^2 = 0%; P = 0.95]. Similar effects were observed in patients assigned to receive calcitriol [MD = -1.40; 95% CI (-4.76, 1.96); P = 0.41], alfacalcidol [MD = -0.69; 95% CI (-6.91, 5.53); P = 0.83], or vitamin D3 [MD = 4.42; 95% CI (-6.09, 14.93); P = 0.41] (Fig. 5A). Such effects were also consistent at lower dose of calcitriol (≤ 0.25 μg/d) [MD = -3.30; 95% CI (-9.05, 2.45); P = 0.26; I^2 = 0%]; at higher dose of calcitriol (≥ 0.25 μg/d) [MD = -0.42; 95% CI (-4.56, 3.71); P = 0.84; I^2 = 0%] (Fig. 5B); at shorter duration of calcitriol usage (2-3 months) [MD = -6.60; 95% CI (-16.05, 2.85); P = 0.17; I^2 = 0%]; or at longer duration of calcitriol usage (4-6 months) [MD = -0.65; 95% CI (-4.25, 2.94); P = 0.72; I^2 = 0%] (Fig. 5C).

eGFR. Only four RCTs reported sufficient data to evaluate the effect of VD on eGFR, involving 290 participants (T/C: 147/143). eGFR was not affected by VD supplementation in DN patients [MD = 2.13; 95% CI (-2.06, 6.32); P = 0.32; I^2 = 0%]. Such effect remained regardless of taking calcitriol [MD = 2.71; 95% CI (-1.83, 7.25); P = 0.24] or vitamin D3 [MD = -1.18; 95% CI (-12.02, 9.66); P = 0.83] (Fig. 6). Further subgroup analysis based on dose or duration was not performed because of limited sample size.

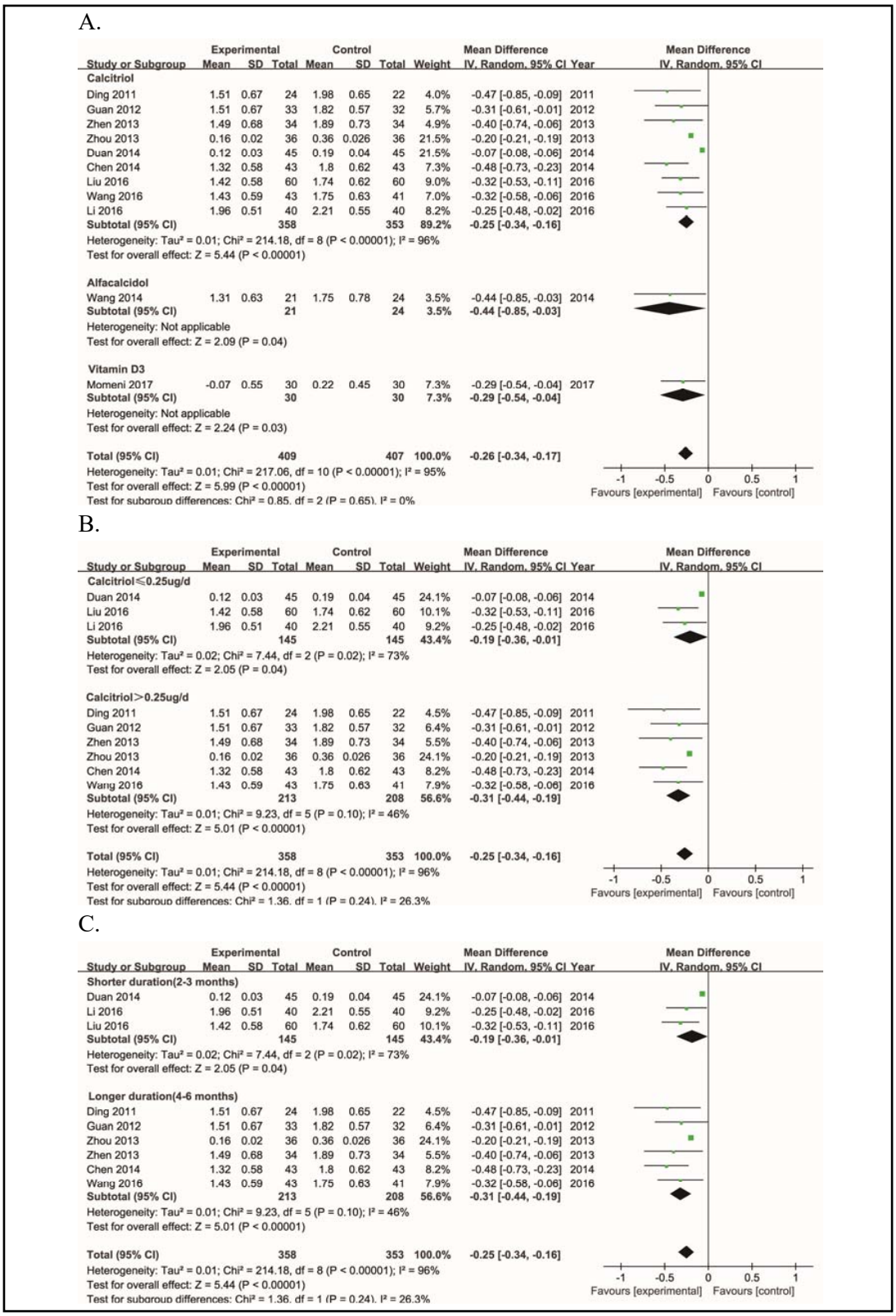

Fig. 3. Effects of VD supplementation on 24-hour urine protein. A. Effect on 24-hour urine protein based on type of VD supplementation. B. Effect on 24-hour urine protein based on dose of calcitriol. C. Effect on 24-hour urine protein based on duration of calcitriol.

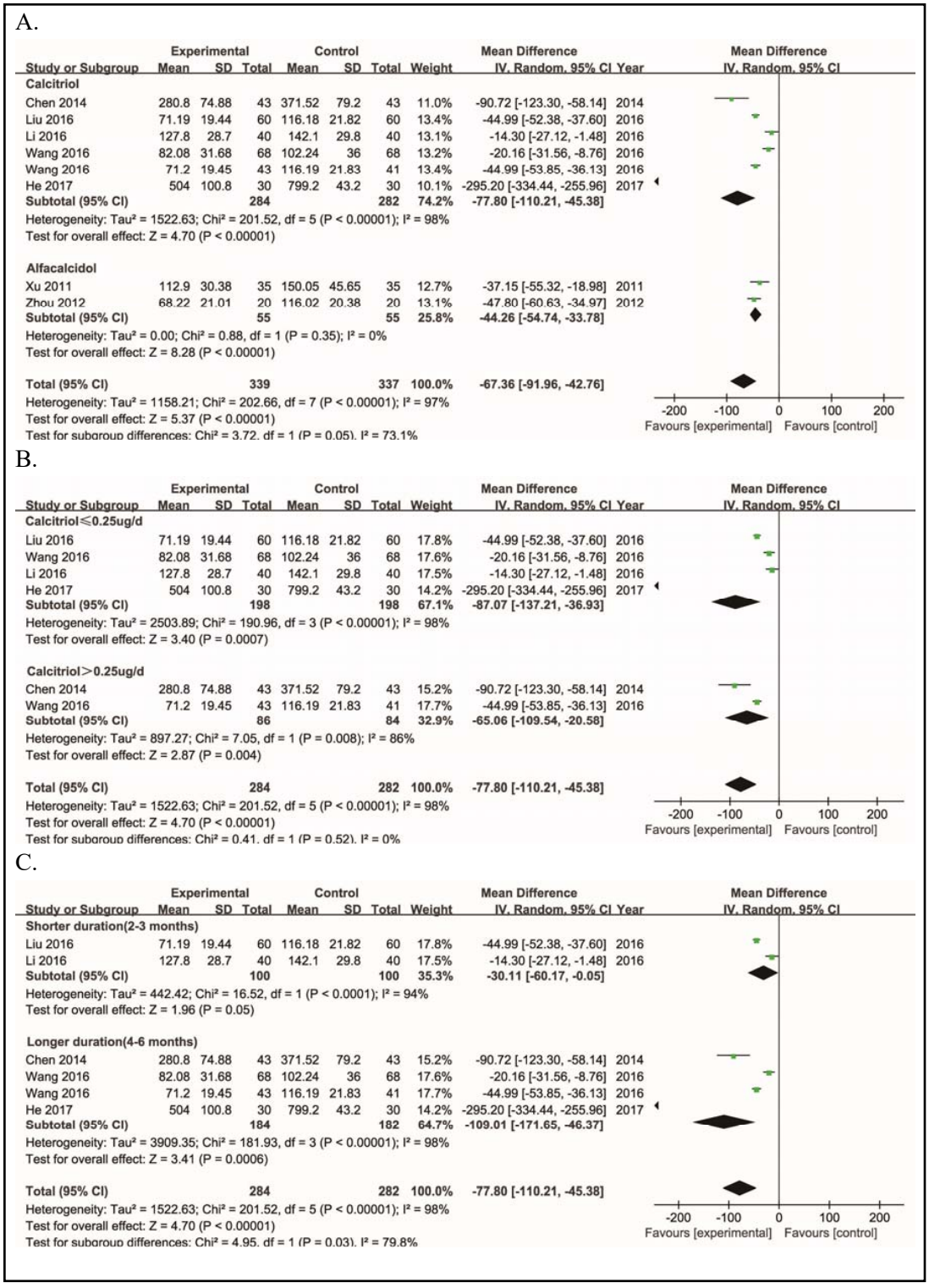

Fig. 4. Effects of VD supplementation on UAER. A. Effect on UAER based on type of VD supplementation. B. Effect on UAER based on dose of calcitriol. C. Effect on UAER based on duration of calcitriol.

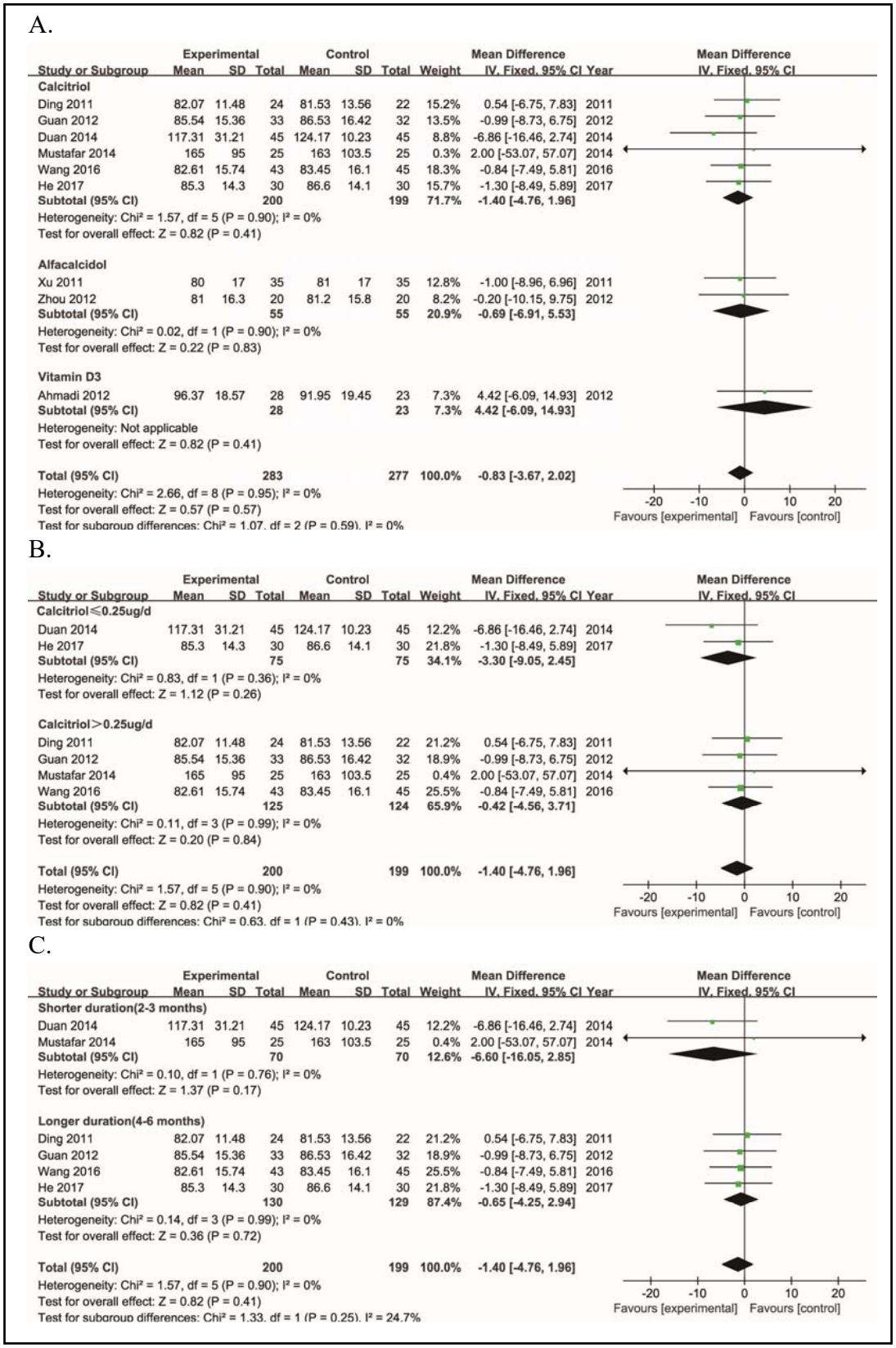

Fig. 5. Effects of VD supplementation on SCr. A. Effect on SCr based on type of VD supplementation. B. Effect on SCr based on dose of calcitriol. C. Effect on SCr based on duration of calcitriol.

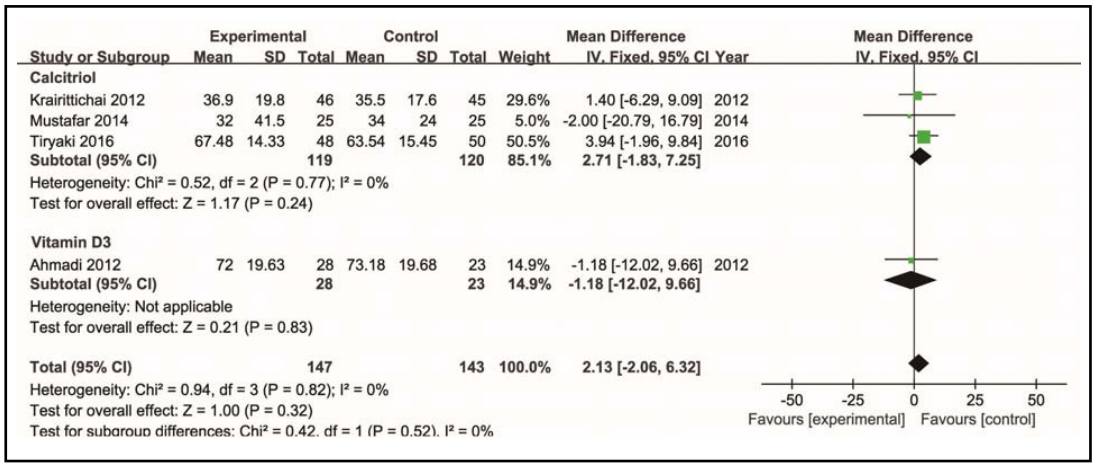

Fig. 6. Effects of VD supplementation on eGFR.

The impact of VD supplementation on indexes of inflammation

hs-CRP. The effect of VD supplementation on hs-CRP was evaluated in seven RCTs involving 534 participants (T/C: 269/265) (Fig. 7A-C). VD supplementation significantly decreased hs-CRP [MD = -0.69; 95% CI (-0.86, -0.53)]; $P < 0.00001$] relative to control with low level of heterogeneity between studies [I^2 = 0%] in DN patients. Subgroup analysis showed significant decrease in patients assigned to receive calcitriol [MD = -0.66; 95% CI (-0.83, -0.49); $P < 0.00001$] or alfacalcidol [MD = -1.03; 95% CI (-1.58, -0.48); P =0.0003] (Fig. 7A). Further subgroup analyses showed that hs-CRP was reduced in response to lower dose of calcitriol (≤ 0.25 μg/d) [MD = -0.76; 95% CI (-1.03, -0.49); $P < 0.00001$] with low study heterogeneity [I^2 = 0%]; higher dose of calcitriol (≥ 0.25 μg/d) [MD = -0.59; 95% CI (-0.82, -0.37); $P < 0.00001$] with low study heterogeneity [I^2 = 0%] (Fig. 7B); shorter duration of calcitriol usage (2-3 months) [MD = -0.63; 95% CI (-1.00, -0.26); P = 0.0008]; and longer duration of calcitriol usage (4-6 months) [MD = -0.67; 95% CI (-0.86, -0.47); $P < 0.00001$] with low study heterogeneity [I^2 = 0%] (Fig. 7C).

TNF-α. Only three RCTs reported TNF-α as primary or secondary outcome measure (Fig. 8), involving 284 participants (T/C: 143/141). Heterogeneity assessment indicated high level of heterogeneity between studies [I^2 = 89%; $P < 0.0001$]. Using random effect model, we found that calcitriol supplementation significantly decreased TNF-α by 56.79 mg/L [MD = -56.79; 95% CI (-77.05, -36.52); $P < 0.00001$] relative to control in DN patients. Subgroup analysis was not performed due to limited sample size.

IL-6. Only three RCTs involving 284 participants (T/C: 143/141) evaluated the impact of calcitriol supplementation on IL-6 (Fig. 9). Heterogeneity assessment indicated low study heterogeneity [I^2 = 0%; P = 1.00]. Meta-analysis performed by the fixed effect model showed that IL-6 was dramatically reduced by 0.73 mg/L in response to VD supplementation [MD = -0.73; 95% CI (-1.03, -0.44); $P < 0.00001$] in DN patients. Subgroup analysis was not performed due to limited sample size.

The impact of VD supplementation on indexes of glycemic control

*HbA1c.*The effect of VD supplementation on HbA1c was evaluated in ten RCTs involving 692 participants (T/C: 348/344) (Fig. 10A-C). VD supplementation did not affect HbA1c in DN patients [MD = 0.01; 95% CI (-0.09, 0.11); P = 0.84] with low level of heterogeneity between studies [I^2 = 0%; P = 0.72]. Such effect remained in patients assigned to receive calcitriol [MD = 0.02; 95% CI (-0.08, 0.12); P = 0.71], alfacalcidol [MD = 0.10; 95% CI (-0.34, 0.54); P = 0.65], or vitamin D3 [MD = -0.24; 95% CI (-0.82, 0.34); P = 0.42] (Fig. 10A). Calcitriol showed no impact on HbA1c regardless of lower dose (≤ 0.25 μg/d) [MD = 0.04; 95% CI (-0.16, 0.24); P = 0.70]; higher dose (> 0.25 μg/d) [MD =0.01; 95% CI (-0.11, 0.13); P = 0.84] (Fig. 10B);

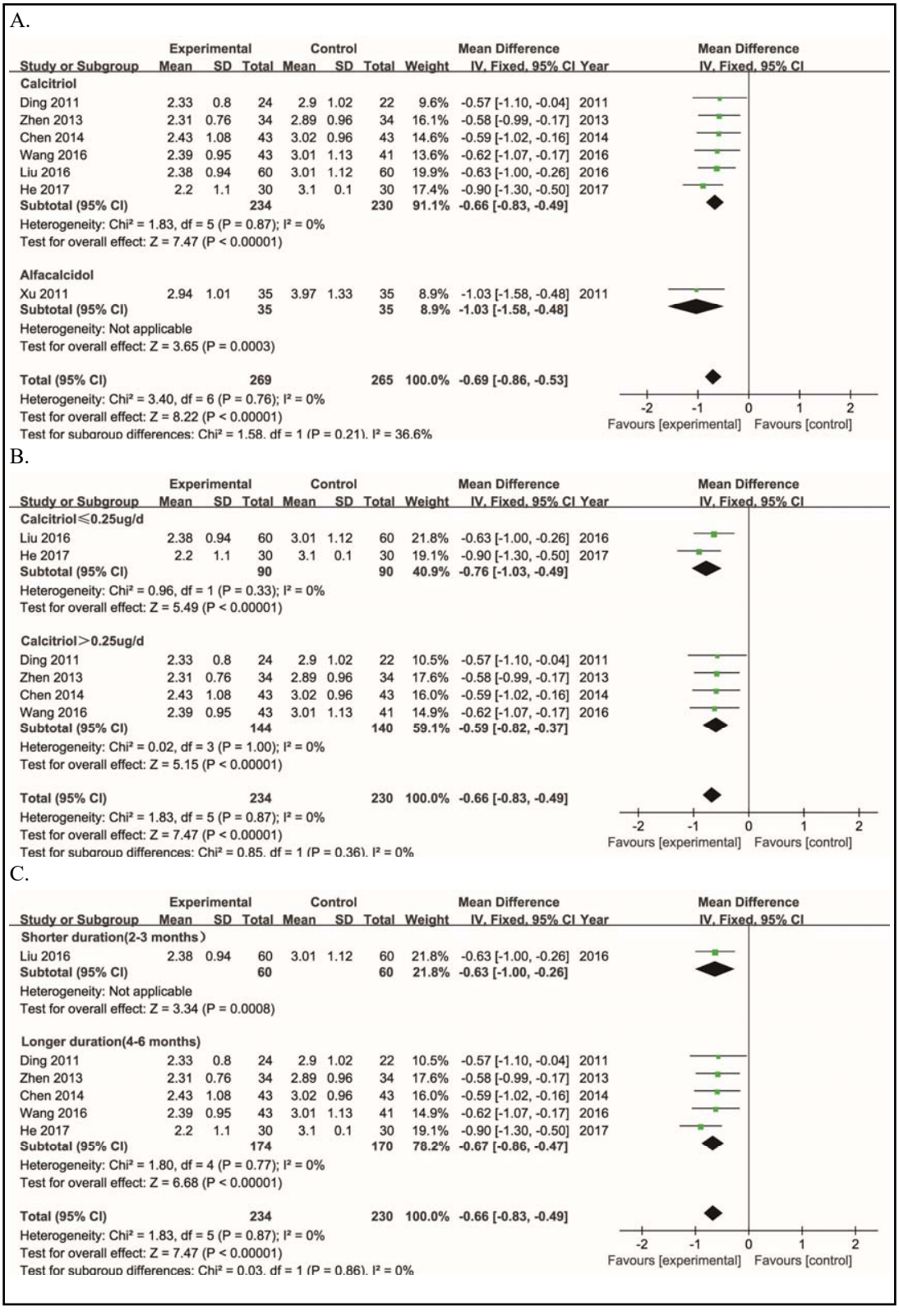

Fig. 7. Effects of VD supplementation on hs-CRP. A. Effect on hs-CRP based on type of VD supplementation. B. Effect on hs-CRP based on dose of calcitriol. C. Effect on hs-CRP based on duration of calcitriol.

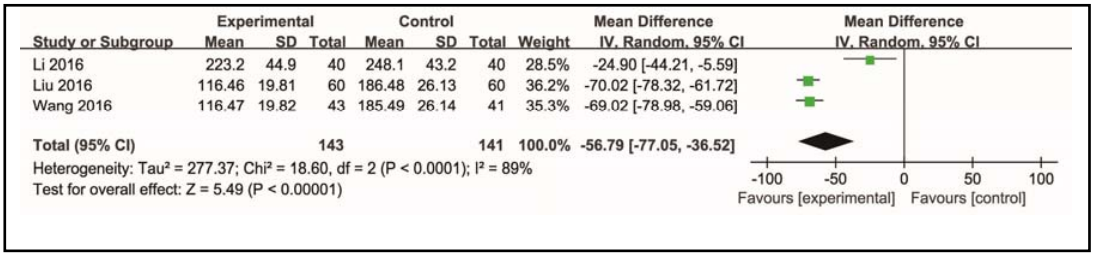

Fig. 8. Effects of VD supplementation on TNF-α.

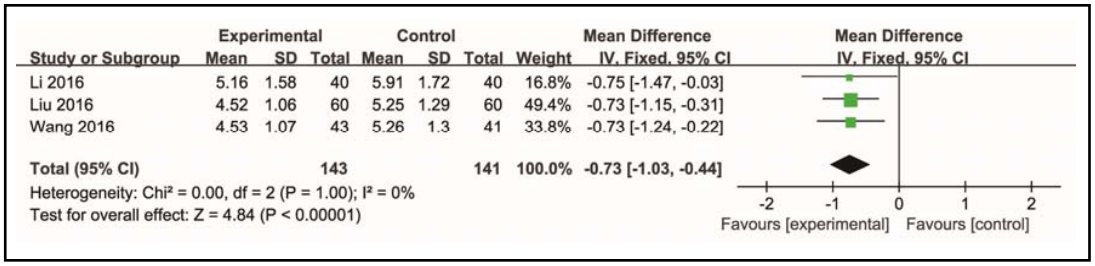

Fig. 9. Effects of VD supplementation on IL-6.

shorter duration of usage (2-3 months) [MD = 0.04; 95% CI (-0.16, 0.24); P = 0.70;] ; or longer duration of usage (4-6 months) [MD = 0.01; 95% CI (-0.11, 0.13); P = 0.84] (Fig. 10C).

FBG

Only three RCTs reported FBG as primary or secondary outcome measure (Fig. 11), involving 230 participants (T/C: 115/115). Heterogeneity assessment indicated low study heterogeneity [I^2 = 0%; P = 0.78]. Using fixed effect model, we found that FBG was not affected by VD supplementation in DN patients [MD = -0.05; 95% CI (-0.29, 0.20); P = 0.70]. Such effect remained in patients assigned to receive either calcitriol [MD = -0.09; 95% CI (-0.37, 0.19); P = 0.53] or alfacalcidol [MD = 0.10; 95% CI (-0.42, 0.62); P = 0.71].

Sensitivity analysis and publication bias

We performed sensitivity analysis on all 20 included RCTs using Leave-One-Out methods. Variations of the combined effects after excluding each indicator variable was relatively small, indicating the robustness of our meta-analytic results. Funnel plots were used in our meta-analysis to evaluate publication bias. Except for studies assessing HbA1c, studies evaluating all other indexes were asymmetrically distributed on the funnel plots, suggesting the presence of publication bias.

Discussion

VD supplementation has long been used in the treatment of chronic kidney disease (CKD), primarily to regulate calcium homeostasis and bone metabolism. Our meta-analytic results demonstrate that supplementation of VD or its analogs could reduce urinary protein excretion and lower the levels of key inflammatory factors, such as hs-CRP, TNF-α and IL-6, suggesting that VD might protect kidney functions and delay DN progression via other pathways. Importantly, these results were consistent in all our included RCTs regardless of the type of VD supplementation, including calcitriol, alfacalcidol and vitamin D3, and regardless of the dose or duration of calcitriol usage.

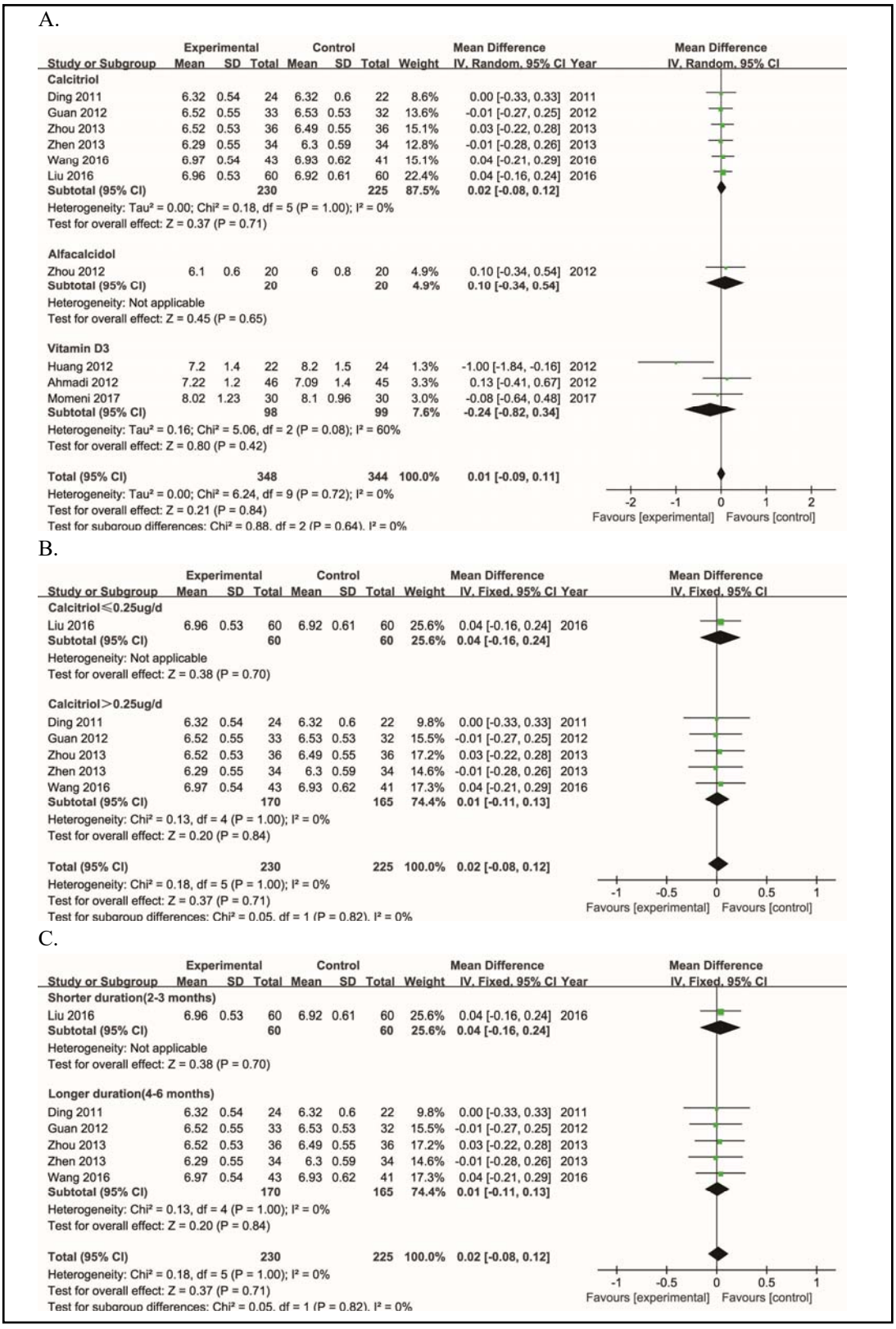

Fig. 10. Effects of VD supplementation on HbA1c. A. Effect on HbA1c based on type of VD supplementation. B. Effect on HbA1c based on dose of calcitriol. C. Effect on HbA1c based on duration of calcitriol.

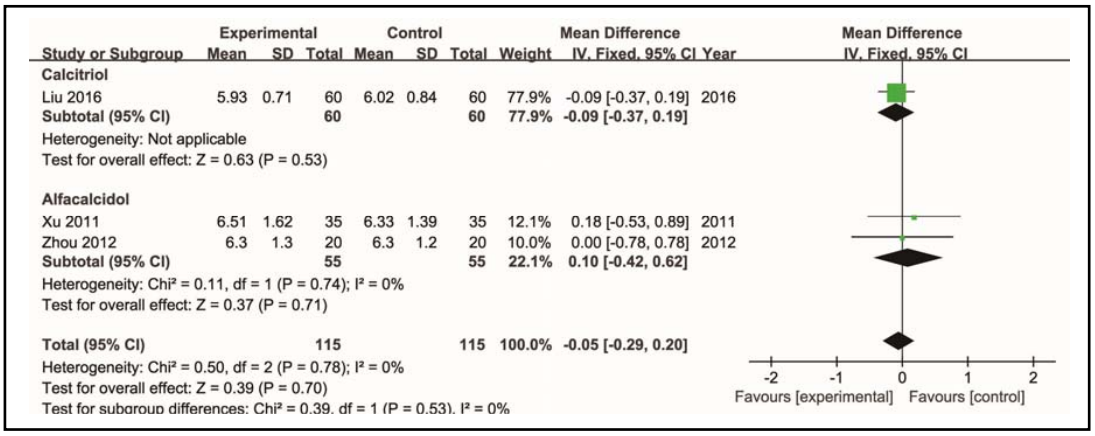

Fig. 11. Effects of VD supplementation on FBG.

Albuminuria reduction is considered as an important factor to predict future renal outcomes [32]. It remains controversial whether VD supplementation could reduce proteinuria and provide clinical benefit to DN patients. Consistent with our results, Zhao J et al. showed that vitamin D3 ameliorates proteinuria and protects DN patients from kidney injury, which is independent of blood pressure and glucose reduction [8]. On the other hand, Derakhshanian H et al. did not find potential benefit of vitamin D supplementation on UACR in DN patients [9]. Several possible factors might affect the results of this meta-analysis: six cross-sectional studies were included in this meta-analysis; the number of patients in some included studies was small; VD supplementation failed to elevate the serum vitamin D level significantly in some included studies. A most recent meta-analysis in CKD patients showed that paricalcitol reduces the risk of cardiovascular events, but does not affect proteinuria level nor protect renal function in CKD patients [33]. Unfortunately, this meta-analysis did not further analyze the data based on the primary causes of CKD (e.g., diabetic nephropathy, hypertentive nephropathy). Our meta-analysis was specifically designed to include patients with diabetic nephropathy and our results demonstrated that VD supplementation, including calcitriol, alfacalcidol and vitamin D3, could reduce urinary protein excretion. However, paricalcitol was not included in our final analysis because the limited studies of paricalcitol in diabetic nephropathy patients could not provide sufficient data for our meta-analysis to proceed.

Our meta-analysis did not to find any evidence to show that VD supplementation decreases SCr or increases eGFR, which is consistent to several other systemic reviews. For instance, Xu et al. found that VD supplementation decreases proteinuria, although it did not significantly change the eGFR in non-dialysis patients [34]. Additionally, Zhang et al. showed in a recent meta-analysis of both CKD and non-CKD patients that vitamin D receptor activators lead to elevation of SCr and decrease creatinine-based measures of eGFR[35]. This result was unexpected because it demonstrated that albuminuria reduction was not associated with renal function improvement. Possible explanations are that other risk factors (such as blood glucose, blood pressure, blood lipids) are correlate with the deterioration of renal function but was not considered in this meta-analysis; that eGFR loss might occur independently of albuminuria or even in the absence of albuminuria in some patients with diabetes [36].

Inflammation is pivotal in the progression of DN [37], which eventually leads to renal fibrosis [38]. A previous meta-analysis demonstrated that VD supplementation improved micro-inflammatory state in patients on hemodialysis [39]. Mansournia's analysis showed that VD supplementation resulted in a significant decrease in hs-CRP in diabetic patients [40]. Eleftheriadis' group found that VD analog paricalcitol decreased basal concentrations of TNF-α and IL-6 in peripheral blood mononuclear cells (PBMCs) of healthy volunteers [41]. Additionally, VD supplementation was able to lower the levels of inflammatory markers,

including TNF-α, IL-6 and ICAM-1, in the serum and urine of type 1 diabetes patients [42]. Our meta-analysis also found that VD supplementation could reduce the levels of key inflammatory factors, including hs-CRP, TNF-α and IL-6, in DN patients, which was consistent with other studies.

It is not clear whether VD supplementation provides benefit on glycemic control based on previous meta-analyses. Naghmeh Mirhosseini et al. found that VD supplementation may significantly reduce FBG and HbA1c and facilitate glycemic control in type 2 diabetic patients [43]. However, Li et al. didn't find that VD supplementation would improve FBG or HbA1c [44]. Our meta-analysis assessed the effects of VD supplementation on glycemic control in DN patients, and showed that levels of FBG or HbA1c were not different between the experimental and the control group. As the number of included studies is relatively small, studies with larger sample size are required to further evaluate the effects of VD supplementation on glycemic control in DN patients.

The limitations of our meta-analysis include: relatively small sample size; varying lengths of follow-up time; varying amounts and forms of VD supplementation; inconsistent treatments among control groups; lack of long-term follow-up results. There is an urgent need for RCTs of larger sample size, placebo-controlled, comprehensive outcome measures, long-term followed-up and multi-centered in order to clarify the real impact of VD supplementation on indexes of renal function, inflammation and glycemic control in DN patients. VD supplementation would become a low-cost and convenient treatment strategy with social benefits in DN patients if a clear conclusion is reached that VD supplementation prevents and treats DN.

Conclusion

The results of this meta-analysis support the use of vitamin D or its analogs to reduce urinary protein excretion and the levels of key inflammatory factors, including hs-CRP, TNF-α and IL-6, although VD supplementation did not have significant influence on SCr, eGFR or glycemic control. As these results are generated from an exploratory meta-analysis without a specifically defined hypothesis, more RCTs that comprehensively evaluate the impact of VD supplementation on indexes of renal function, inflammation and glycemic control in DN patients are required in order to reach conclusive results.

Disclosure Statement

All authors declare that there is no conflict of interest.

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