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Efficacy of Vitamin D_3 in Patients With Diabetic Nephropathy: An Updated Meta-Analysis

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Abstract

Context: Diabetic nephropathy is a common complication of diabetes mellitus with a higher incidence. Renin-angiotensin system blockers, as the main treatment for patients with diabetic kidney disease, can not only reduce albuminuria, but also lead to hyperkalaemia and creatinine. Therefore, additional protective therapeutic interventions are needed.

Evidence Acquisition: An electronic literature search was conducted in international and domestic databases including PubMed, Embase, CNKI, Scopus, Index Copernicus, DOAJ, and Wanfang database for trials up to January 2017. The search terms used were as follow: "Diabetic Nephropathies", "vitamin D_3", "Cholecalciferol", "Calcitriol", "Alfacalcidol", "Paricalcitol", and "Randomized Controlled Trial". Quality assessments were evaluated with the Newcastle-Ottawa Quality Assessment Scale. Data were extracted by 2 independent reviewers (TJL and WGL). For all analysis, the standard mean difference (SMD) or odds ratio (OR) with 95% confidence intervals (CIs) were calculated, and heterogeneity of the studies was analyzed using I^2 statistics.

Results: Twenty-four studies were (1,978 patients) identified in the literature retrieve process. The assessment scores indicated that all the admitted studies were reliable with scores ranging from 6 to 9. The pooled results indicated that vitamin D_3 had a significant effect in reducing albuminuria (MD = -0.23, 95% CI: -0.30, -0.15) and that the vitamin D_3 group had a low ratio of urinary microalbumin to creatinine than the control group (SMD = -0.49, 95% CI: -0.90, -0.08). The results also revealed that vitamin D_3 group had a lower hs-CRP than the control group (MD = -0.80, 95% CI: -1.26, -0.34).

Conclusions: Based on the evidence of this study, vitamin D_3 could be suggested as a recommended drug for patients with diabetic nephropathy in clinical practice.

Keywords: Vitamin D_3, Meta-Analysis, Urinary Albumin/Creatinine Ratio

1. Context

Diabetic nephropathy (DN) is a common complication of diabetes mellitus (DM), usually accounting for chronic renal failure in many countries (1). The prevalence of diabetic kidney disease is 30% among patients with type I DM, and about 20% to 50% of type II DM patients would probably be accompanied with renal lesions (2). Although it has been suggested that abnormalities of renal hemodynamics, hyperglycemia-induced metabolic disorders, and the imbalance of vasoactive substances may be involved in the development of diabetic kidney disease, the mechanism responsible for diabetic nephropathy remains incomplete, and thus the corresponding optimal therapy is undecided (3).

Multiple agents have been used to delay the progression of diabetic nephropathy including beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB). In accordance with several large-scale randomized controlled trials (RCTs), ACEI and ARB have been proposed as the first line agents for treating diabetic nephropathy because of their role in reducing proteinuria (4). However, these agents also contribute to elevated levels of hyperkalaemia and creatinine, finally limiting their actions to improve kidney function (5). Therefore, additional interventions that are against diabetic nephropathy are needed.

Vitamin D_3 belongs to fat-soluble secosteroids, and its major activating mode is shown as $1,25(OH)_2D_3$, whose activity is mediated by vitamin D receptor (VDR). Moreover, $1,25(OH)_2D_3$-VDR has manifold physiological and pathological functions including regulation of mineral metabolism, renal function, and cardiovascular function (6). Importantly, Mattila et al. found that high vitamin D level could significantly lower the risk of DM, and Gur-

soy et al. also reported that vitamin D deficiency was related to development of DN (7, 8). Therefore, the above contents provide solid evidence that vitamin D might serve as a novel breakout for preventing and treating DN.

Nonetheless, the results of interventional experiments exploring the efficacy of vitamin D on DN are controversial and the renoprotective effects of vitamin D have not yet been clinically demonstrated. Therefore, this study aimed at prospectively evaluating the efficacy and safety of vitamin D and their analogues including calcitriol, alfacalcidol, and paricalcitol for DN patients.

2. Evidence Acquisition

2.1. Search Strategy

Electronic databases (PubMed, Embase, Scopus, Index Copernicus, DOAJ, CNKI, and Wanfang) were searched, and randomized clinical trials that investigated vitamin D_3 for DN patients and published before January 2017 were included in this study. The search terms used were as follow: "Diabetic Nephropathies", "vitamin D_3", "Cholecalciferol", "Calcitriol", "Alfacalcidol", "Paricalcitol", and "Randomized Controlled Trial". Additional related studies were added manually after checking the reference lists of all qualified publications including relevant meta-analyses and systematic reviews.

2.2. Inclusion and Exclusion Criteria

Trials had to meet the following criteria: (i) the DN patients had to be 18 years or older; being diagnosed with DN within a minimum of 4 weeks; (ii) the interventions in the studies had to include vitamin D_3 or its analogs; (iii) estimated glomerular filtration rate (eGFR) had to be > 20 mL/min per 1.73 m^2 or serum creatinine as < 3 mg/dL; and (iv) microalbuminuria, or macroalbuminuria (urinary albumin/creatinine ratio (UACR) > 3 mg/mmol, or UAER > 0.2 mg/min) had to be confirmed. Major exclusion criteria were as follow: (i) animal experiments and cell-line studies; (ii) editorial, commentaries, review articles and case reports; (iii) studies without relevant or sufficient data.

2.3. Outcomes and Data Extraction

The primary clinical outcomes included 24-hour proteinuria and urinary albumin-creatinine ratio (UACR), while the secondary measures were related to high sensitivity C reactive protein (hs-CRP), glycosylated hemoglobin (HbA1c), serum calcium, and serum creatinine. Safety outcomes were presented as adverse events. Two reviewers extracted the data from eligible studies independently. If some discrepancies were present, then, the third reviewer resolved the disagreements. The extracted information mainly included baseline characteristics (including age, type of diabetes, and concomitant drug), type of interventions (including type and dose of vitamin D_3 and therapy duration), and outcome measures.

2.4. Quality Assessment

Quality assessment was independently performed by 2 reviewers using Newcastle-Ottawa quality assessment scale, which consists of 9 questions in 3 sections (selection, comparability, and exposure section). The quality of the studies was evaluated by examining 9 questions and each question had to be answered with "yes", "no", or "unclear". An answer of "yes" got the score of 1, indicating a low risk of bias, whereas an answer of "no" or "unclear" gained a score of "0", suggesting a high risk of bias may exist.

2.5. Statistical Analysis

This meta-analysis was conducted to perform direct comparisons between the intervention and placebo. Interstudy heterogeneity was evaluated by the I^2 test when I^2 > 50% random effect model was used, otherwise, fixed-effects model was adopted. The dichotomous variables were evaluated by mean difference (MD) or standard mean difference (SMD), with 95% confidential interval (CI). Continuous variables were assessed by odds ratio (OR), with 95% confidential interval. Subgroup analysis by intervention (whether ACEI/ARB was used or not) was performed. Sensitivity analysis was performed to find the source of heterogeneity and evaluate whether the results could be significantly affected. All the analyses were conducted by R 3.2.3 software.

3. Results

The retrieved literature included 158 citations, 83 of which were excluded after reviewing their titles and abstracts. A total of 75 articles were available for the process of full text screening and 24 studies were finally identified for this meta-analysis after considering the inclusion and exclusion criteria (Figure 1) (9-31). These eligible studies were published during 2010 and 2017 and focused on the efficacy of vitamin D3 or its analogues including alfacalcidol, calcitriol, cholecalciferol, and paricalcitol for DN patients.

As 3 studies had a multiple-group design, at last, 26 trials were collected; 15 trials were designed to compare vitamin D_3 or its analogs with placebo, while the rest trials compared vitamin D_3 or its analogues with ACEI/ARB and ACEI/ARB. Among the aggregate 1978 patients, 1478 (74.72%) were diagnosed with Type 2 diabetes with nephropathy, 45 (2.27%) were diagnosed with Type 1 diabetes, and the rest

Table 1. The Main Characteristics of Included Studies

Author	Year	Country	Disease	Type of Diabetic	Concomitant Drug	Patients	Age	Period	NOS Score
Momeni	2017	Iran	Diabetic nephropathy + D deficient	2	Conventional therapy	57	NR	8 weeks	8
Shi	2016	China	Diabetic nephropathy	NR	Conventional therapy	124	59.32	8 weeks	9
Tiryaki	2016	Turkey	Diabetic nephropathy	2	Conventional therapy	98	51	24 weeks	8
Munisamy	2016	Malaysia	Diabetic nephropathy	2	Conventional therapy	60	56.85	6 months	7
Thethi	2015	USA	Diabetic nephropathy	2	Conventional therapy	60	62.5	3 months	7
Joergensen	2015	Denmark	Diabetic nephropathy	1	RAAS-blocking treatment and diuretics	45	57	12 weeks	8
Mustafar-a	2014	Malaysia	Diabetic nephropathy + D deficient	2	Conventional therapy	31	53.5	12 weeks	7
Mustafar-b	2014	Malaysia	Diabetic nephropathy + D deficient	2	Conventional therapy	31	53.5	6 weeks	7
Zhan	2013	China	Diabetic nephropathy	NR	Conventional therapy	68	52.75	6 months	7
Pang	2013	China	Diabetic nephropathy	NR	Conventional therapy	80	52.05	2 months	9
Ni	2013	China	Diabetic nephropathy	2	Oral hypoglycemic drugs/insulin	60	59.21	4 weeks	7
Zhou	2013	China	Diabetic nephropathy	NR	Oral hypoglycemic drugs/insulin	72	45.62	6 months	8
Zhou-a	2013	China	Diabetic nephropathy	2	Oral hypoglycemic drugs	42	52.13	3 months	7
Zhou-b	2013	China	Diabetic nephropathy	2	Oral hypoglycemic drugs	42	52.13	3 months	7
Ahmadi	2013	Iran	Diabetic nephropathy + D deficient	2	ACEI/ARB	60	57.7	12 weeks	9
Guan	2012	China	Diabetic nephropathy	NR	Oral hypoglycemic drugs/insulin	65	53.9	6 months	6
Zhu	2012	China	Diabetic nephropathy	2	Oral hypoglycemic drugs	138	57	3 months	8
Shui	2012	China	Diabetic nephropathy	2	Oral hypoglycemic drugs + insulin	30	59.21	3 months	7
Zhou	2012	China	Diabetic nephropathy	2	NR	40	50.12	12 weeks	7
Krairittichai	2012	Thailand	Diabetic nephropathy + D deficient	2	Standard treatment	91	60.75	16 weeks	8
Huang	2012	China	Diabetic nephropathy	2	Conventional therapy	46	56.73	6 months	7
Xu	2011	China	Diabetic nephropathy	2	Novolin 30R	70	50.8	12 weeks	8
Ding	2011	China	Diabetic nephropathy	NR	Oral hypoglycemic drugs/insulin	46	52.04	6 months	6
Lu	2011	China	Diabetic nephropathy	2	Insulin	82	50.5	12 weeks	8
Xu	2010	China	Diabetic nephropathy	2	Insulin	80	50.63	12 weeks	7
de Zeeuw-a	2010	Multinational	Diabetic nephropathy	2	Conventional therapy	180	64.33	24 weeks	9
de Zeeuw-b	2010	Multinational	Diabetic nephropathy	2	Conventional therapy	180	64.33	24 weeks	9

Abbreviations: NR, none reported; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker

of 455 patients (23.00%) were not classified within DN. Besides, most patients continued conventional therapy after the intervention including insulin, ACEI/ARB, and oral hypoglycemic drugs. The design features of each trial, patients' characteristics, and outcomes are summarized in Tables 1 and 2.

A total of 14 studies recorded the change of 24-hour proteinuria, and their results indicated that vitamin D_3 has a significant effect on reducing albuminuria (MD = -0.23, 95% CI: -0.30, -0.15) (Figure 2). The subgroup analysis confirmed the efficacy of vitamin D_3 when it was compared with placebo (MD = -0.15, 95% CI: -0.23, -0.06) or ACEI/ARB (MD = -0.49, 95% CI: -0.72, -0.26). Furthermore, the vitamin D_3 group had a low ratio of urinary microalbumin to creatinine (ie, UACR) than the control group (SMD = -0.49, 95% CI: -0.90, -0.08) (Figure 3). Compared with ACEI/ARB, vitamin D_3 had a better performance in lowering UACR (SMD = -1.86, 95% CI: -2.61, -1.10), while vitamin D_3 tended to reduce UACR compared to placebo (SMD = -0.33, 95% CI: -0.70, 0.03). Of the trials, 7 had been involved in hs-CRP, showing that vitamin D_3 group had a notably lower hs-CRP than the control group (MD = -0.80, 95% CI: -1.26, -0.34) (Figure 4). When compared with placebo, the subtotal results had a similar implication of vitamin D_3's effect (MD = -0.91, 95% CI: -1.15, -0.67), yet no significant difference was found in the comparison between vitamin D_3 and ACEI/ARB.

In the 12 trials that studied serum calcium, vitamin D_3 elevated serum calcium level in either the total results or the subtotal results compared with placebo (MD = 0.04, 95% CI: 0.01, 0.06; MD = 0.07, 95% CI: 0.01, 0.12). No difference was obtained between the serum calcium level in vitamin D_3 group and ACEI/ARB group. Figure 6 demonstrates that there was no difference in the occurrence of adverse events between vitamin D_3 group and ACEI/ARB group (OR = 1.06, 95% CI: 0.68, 1.64). Also, no significant difference was found in HbA1c and serum creatinine (supplementary file Appendix 1 and supplementary file Appendix 2).

Potential publication bias of the included studies was assessed by the funnel plot, revealing no statistical significance in the 6 outcomes (all p-values > 0.05) (Figure 7).

Table 2. The Intervention and Endpoint Information of Included Studies

Study ID	Treatment	Control	Endpoints
Momeni 2017	Cholecalciferol	Placebo	24-hour proteinuria; HbA1c
Shi 2016	Calcitriol	Placebo	HbA1c
Tiryaki 2016	Calcitriol	Placebo	UACR
Munisamy 2016	Alfacalcidol	Placebo	hs-CRP; serum calcium
Thethi 2015	Paricalcitol	Placebo	24-hour proteinuria; serum creatinine
Joergensen 2015	Paricalcitol	Placebo	24-hour proteinuria; adverse events
Mustafar-a 2014	Calcitriol	Placebo	Urine PCI; serum calcium; serum creatinine
Mustafar-b 2014	Calcitriol	Placebo	Urine PCI; serum calcium; serum creatinine
Zhan 2013	Calcitriol	Placebo	24-hour proteinuria; hs-CRP; serum calcium; HbA1c
Pang 2013	Calcitriol + Telmisartan	Telmisartan	24-hour proteinuria; serum calcium; HbA1c; Serum creatinine; adverse events
Ni 2013	Calcitriol + Fosinopril	Fosinopril	24-hour proteinuria; adverse events
Zhou 2013	Calcitriol + Irbesartan	Irbesartan	24-hour proteinuria; serum calcium; HbA1c; adverse events
Zhou-a 2013	Calcitriol	Placebo	hs-CRP; HbA1c
Zhou-b 2013	Calcitriol + Irbesartan	Irbesartan	hs-CRP; HbA1c
Ahmadi 2013	Cholecalciferol	Placebo	UACR; serum calcium; HbA1c; serum creatinine; adverse events
Guan 2012	Calcitriol + Telmisartan	Telmisartan	24-hour proteinuria; serum calcium; HbA1c; serum creatinine; adverse events
Zhu 2012	Calcitriol	Placebo	24-hour proteinuria; hs-CRP; adverse events
Shui 2012	Calcitriol + Valsartan	Valsartan	24-hour proteinuria; adverse events
Zhou 2012	Calcitriol + Telmisartan	Telmisartan	UAER; serum calcium; HbA1c; serum creatinine
Krairittichai 2012	Calcitriol	Placebo	UPCR; adverse events
Huang 2012	Cholecalciferol	Placebo	Serum calcium; HbA1c
Xu 2011	Alfacalcidol	Placebo	hs-CRP; serum creatinine; adverse events
Ding 2011	Calcitriol	Placebo	24-hour proteinuria; hs-CRP; serum calcium; HbA1c; serum creatinine; adverse events
Lu 2011	Calcitriol + Fosinopril	Fosinopril	24-hour proteinuria; adverse events
Xu 2010	Alfacalcidol + Benazepril	Benazepril	24-hour proteinuria; serum calcium; serum creatinine; adverse events
de Zeeuw-a 2010	Paricalcitol	Placebo	24-hour proteinuria; UACR; adverse events
de Zeeuw-b 2010	Paricalcitol	Placebo	24-hour proteinuria; UACR; adverse events

Abbreviations: UACR, urinary albumin-creatinine ratio; hs-CRP, high sensitivity C reactive protein; Urine PCI, urine protein creatinine index; HbA1c, glycosylated hemoglobin; UPCR, urine protein-creatinine index

Sensitive analysis indicated that the results would not be significantly affected after omitting each individual study (supplementary file Appendix 3).

4. Discussion

It has been widely accepted that vitamin D_3 functions in multiple approaches to protect kidneys of DN patients including antagonism of inflammatory responses, restraint of renin-angiotensin system (RAS), and mesangial cell proliferation, reduction of proteinuria, prevention of glomerular hypertrophy, as well as improvement of tubulointerstitial fibrosis (8). Our study indicated that vitamin D_3 has a remarkable renoprotective effect by reducing 24-hour proteinuria and lowering the ratio of urinary albumin to creatinine, and alleviating hs-CRP.

In fact, elevated AGT expressions in the state of high glucose would lead to increased synthesis of Ang II, whose contractile effects on afferent arteriole of glomerulus was smaller than those on revehent artery. Thus, hemodynamic changes featured by high pressure, hypertransfusion, and high filtration at the early stage of DM appeared, which became the vital parameter inducing DN development. Vitamin D_3 could serve to reduce composition of Ang II through reduction of the activity of renin gene promoter, upgradation of blood calcium levels to reverse hyperparathyroidism, and blocking of NF-kB signal transduction. Besides, after examining male Sprague-Dawley rats that received total resection of kidney with 3 ng/100g vitamin D_3, deregulated desmin, proliferating cell nuclear antigen (PCNA), and p27 expressions were observed, and augmented glomerular size was found to recover with alleviated proteinuria, suggesting that vitamin D_3 could relieve progression of chronic renal failure and restrain renal growth through targeting sertoli cell and mesangial cell (32). Furthermore, active vitamin D_3 was also demonstrated to be correlated with downregulated

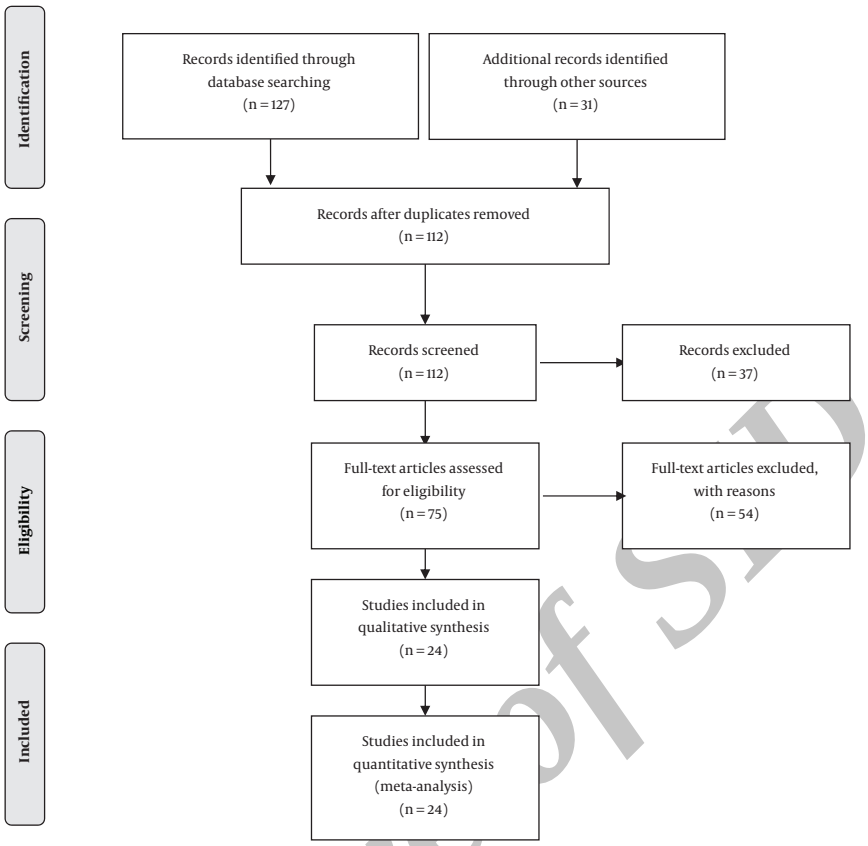


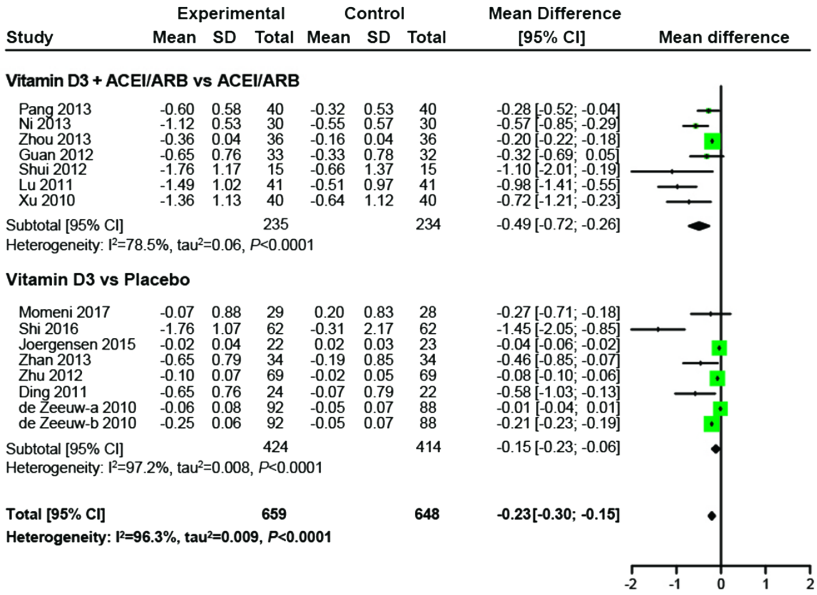
Figure 1. Literature Selection Flow Chart

expressions of inflammatory factors including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (33). Due to the far-ranging mechanisms of vitamin D_3, it displayed its protective role for kidney from initial treatments of diet, decreasing sugar, and reducing proteinuria. For instance, during the process of drug therapy, one randomized and double-blind study documented that vitamin D_3 could clinically cut down urinary protein levels of DN patients, and this action was not dependent on such drugs as ACEI (34). Moreover, by examining DN veterans, who did not undergo dialysis, it was found that they can elongate their life expectancy and simultaneously lower the incidence of complications by using vitamin D_3 (35). In the course of replacement therapy, an investigation comparing 61 children, who were undergoing dialysis and taking vitamin D_3, with 40 age-matched children indicated that vitamin D3 might protect patients' vasculature system by regulation of calcic/phosphor and anti-inflammatory action (36).

As for the combined therapy of ACEI and ARB, they appeared to repress the production of Ang II, which could contribute to vessel contraction. To be specific, ACEI could hold up the conversion of Ang I to Ang II by suppressing the activity of angiotensin converting enzyme (37). Simultaneously, ACEI might enable activity of bradykinin to last long and alter renal hemodynamics, delaying fall of glomerular filtration rate (GFR) (37). Moreover, the interdiction of RAS by ACEI was suggested to restrain production and activity of TGF-β1 within nephridial tissues, which caused sclerosis and fibrosis of glomerular (38-40). Clinical studies also confirmed the meaningful role of ACEI (eg, benazepril and captopril) in doubling blood creatinine levels and improving prognosis of DN patients (41). Nonetheless, as production of Ang II was featured by multiple sources and channels, ACEI could merely restrain the channel of Ang II conversion enzyme. In addition, long-term use of ACEI would lift the responsiveness of renin activity and make Ang II to recur.

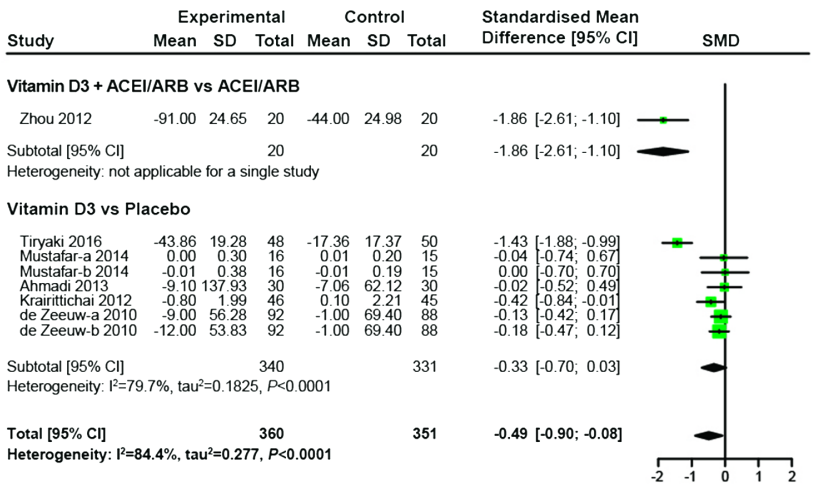
Considering the limitations of ACEI, ARB was also used as the combined therapy because it blocked the adverse effects of Ang II within renal through specifically uniting with AT1 receptor of Ang II, which reduced the preva-

Figure 2. Forest Plot of 24-Hour Proteinuria Change in Patients With Diabetic Nephropathy



The mean difference from each study is represented by square, and the confidence interval is indicated by error bars. The subtotal and overall odds ratio is signified by rhombus.

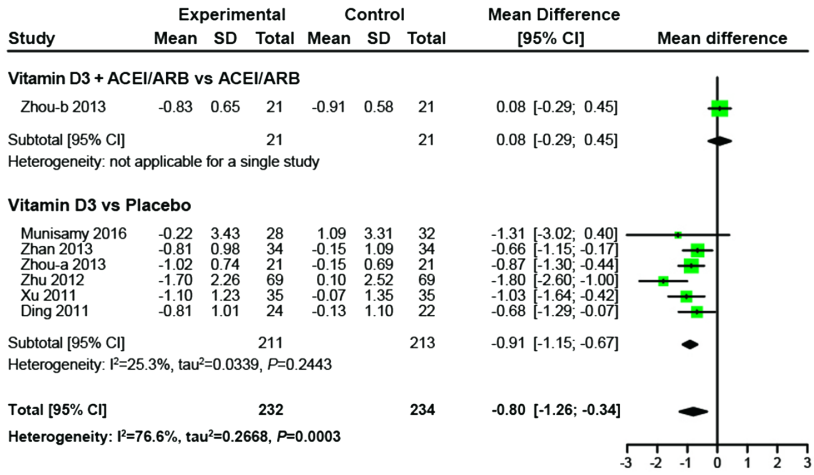
Figure 3. Forest Plot of Urinary Albumin-Creatinine Ratio Change in Patients With Diabetic Nephropathy



The standard mean difference from each study is represented by square, and the confidence interval is indicated by error bars. The subtotal and overall odds ratio is signified by rhombus.

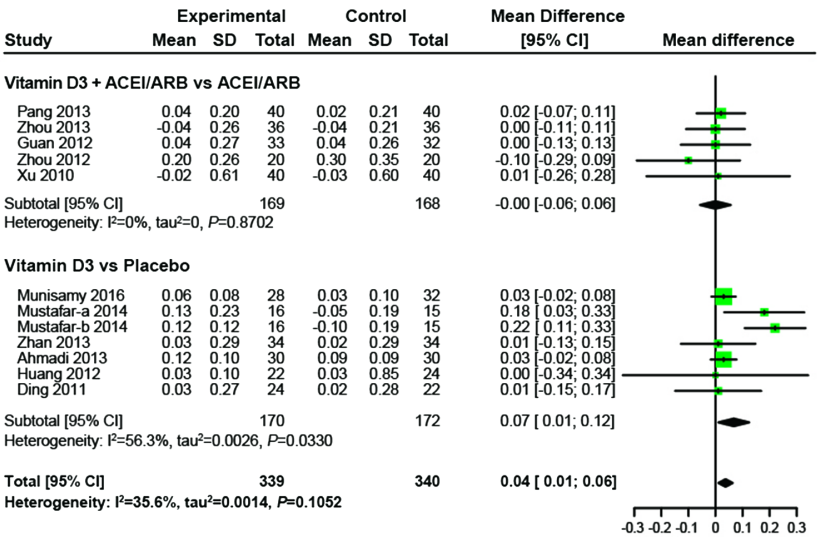
lence of side effects for not affecting the kinin system (eg, edema). Besides, ARB indirectly facilitated combination of Ang II with AT2, by vasodilation (blood vessels) and lowering blood pressure (42). Moreover, ARB (losartan) can boost the excretion of uric acid by kidney, preventing damages imposed by hyperuricemia on kidney (43). The combined treatment efficacy of AECI and ARB has been clinically explored and found to be more superior to AECI or ARB alone, yet certain scholars did not support the idea (44, 45).

Figure 4. Forest Plot of High Sensitivity Creactive Protein Change in Patients With Diabetic Nephropathy



The mean difference from each study is represented by square, and the confidence interval is indicated by error bars. The subtotal and overall odds ratio is signified by rhombus.

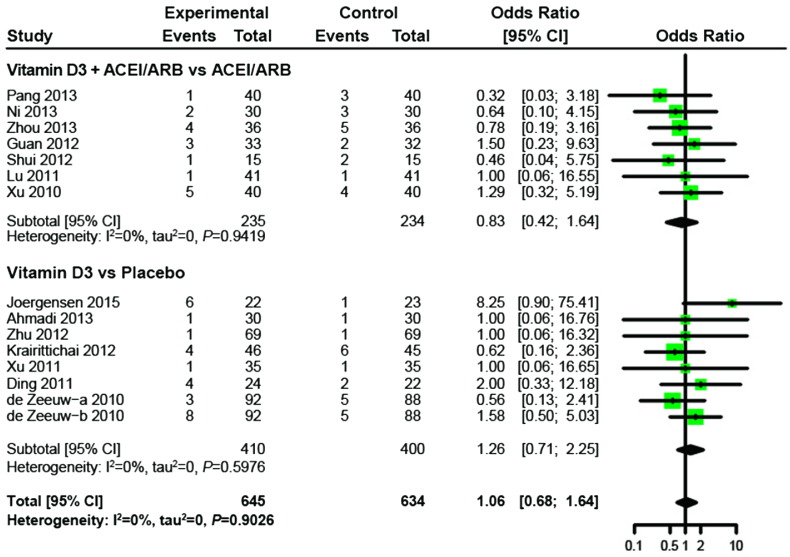
Figure 5. Forest Plot of Serum Calcium Change in Patients With Diabetic Nephropathy



The mean difference from each study is represented by square, and the confidence interval is indicated by error bars. The subtotal and overall odds ratio is signified by rhombus.

After comprehensively exploring the mechanisms of action among vitamin D_3, AECI, and ARB, it was not hard to discover that vitamin D_3 acted in more channels than AECI and ARB to fight against DN. Moreover, vitamin D_3 is a natural ingredient found within organisms, which could account for less side effects of vitamin D_3 than AECI and ARB. This meta-analysis was an updated pooled analysis, which included the latest articles published in 2016 and 2017. Furthermore, this meta-analysis contained 7 outcomes to present the renoprotective effect of vitamin D, which was more comprehensive than the existed meta-analysis. Lastly, in this analysis, we not only compared the difference between vitamin D and placebo, but also took AECI and ARB into consideration. In clinical practice,

Figure 6. Forest Plot of Adverse Events in Patients With Diabetic Nephropathy



The odds ratio from each study is represented by square, and the confidence interval is indicated by error bars. The subtotal and overall odds ratio is signified by rhombus.

we cannot neglect the mutual function of treatments of patients with diabetic nephropathy. However, there were some limitations in this study. Firstly, all the 24 studies took active substance or analogs of vitamin D_3 as intervention; secondly, patients with Type 1 diabetes had only been enrolled in Joergensen's study, and 5 studies had not reported the type of their diabetic patients, and 4 trials had been grouped based on the different dose of drugs; and thirdly, the concomitant drugs varied in the 24 studies.

5. Conclusions

In summary, vitamin D_3 is a promising therapy for diabetes patients with proteinuria. Based on the evidence of this study, vitamin D_3 is suggested as a recommended drug for diabetic nephropathy in clinical practice. Nonetheless, large and more randomized clinical trials should be conducted to confirm and elucidate the efficacy and mechanism of vitamin D_3.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

None.

Footnote

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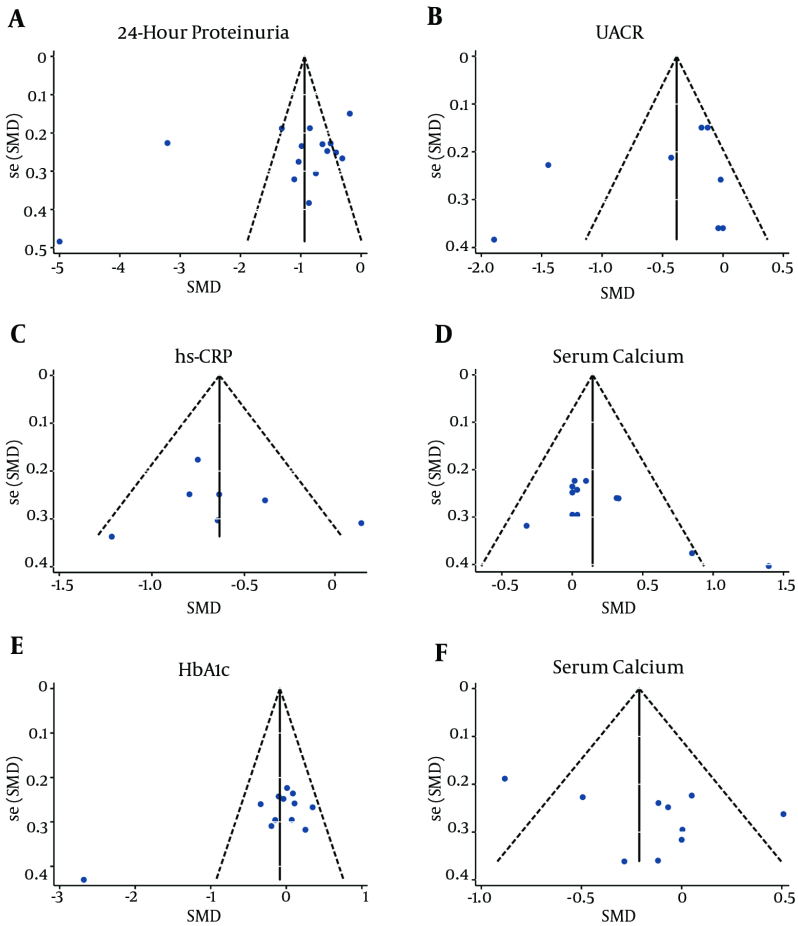

Figure 7. Funnel Plot of Included Studies in Each Outcomes

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