META-ANALYSIS

Effect of Vitamin E on Diabetic Nephropathy: A Meta-Analysis

Zhenjie Jin, MD; Jia Sun, BD; Wen Zhang, BD

ABSTRACT

Background • Diabetes nephropathy has always been one of the main causes of chronic kidney disease and end-stage kidney disease (ESRD), and diabetes nephropathy accounts for about 40% of ESRD cases. Vitamin E can effectively reduce urinary microalbumin, urinary albumin excretion rate and serum nitric oxide level in patients with type 2 diabetes nephropathy.

Methods • The computer retrieves four databases to obtain controlled trials on the effects of vitamin E in patients with diabetic nephropathy. After a rigorous literature quality evaluation, data analysis was performed using Stata software. Study Design Type Published controlled trials on the effects of vitamin E in patients with diabetic nephropathy. However, the animal trials were excluded. The intervention group received vitamin E in the treatment of patients with diabetic nephropathy, and the control group received a placebo in the treatment of patients with diabetic nephropathy. Outcome indicators patients with diabetic nephropathy; According to research, the assessment tools for the effects of vitamin E in patients with diabetic nephropathy are: (1) HbA_{1c} (Glycated hemoglobin,%); (2) EGFR (mL/min 1.73 m^2); (3) Serum creatinine (μmol/L); (4) Urea (mmol/L); (5) Systolic BP (mmHg); (6) Diastolic BP (mmHg).

Results • 5 studies were ultimately included in this meta-analysis. 5 studies reported the glycosylated hemoglobin (HbA_{1c}) of the test group and the control group, which was significantly lower (SMD: -0.17; 95% Cl: -0.26,-0.07; $P <$ .01) than the control group. Meta-analysis showed that the Serum creatinine of the test group was also significantly lower (SMD: -11.20; 95% Cl: -12.89,-9.51; $P <$ .01) than the control group. EGFR of the test group had no significant statistical significance (SMD: -0.90; 95% Cl: -13.30,11.49; P = .886) than the control group. Meta-analysis showed that the urea of the test group had no significant statistical significance(SMD: -0.57; 95% Cl: -1.58,0.45; P = .275). The systolic BP (SMD: -3.95; 95% Cl: -9.79,1.88; P = .184) and Diastolic BP (SMD: 0.26; 95% Cl: -0.75,1.27; P = .617) are also consistent with the group.

Conclusion • The results of this study suggest that vitamin E may be effective on in patients with diabetic nephropathy, as evidenced by HbA_{1c} and Serum creatinine, and the above conclusions need to be verified by more high-quality studies. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Diabetes refers to the metabolic disorder caused by human genes and environmental factors, resulting in insulin insensitivity, insulin reduction and other biological system damage.[1] The incidence and number of adult diabetes in low- and middle-income countries have increased rapidly in comparison with high-income countries.[1] In the past 30 years, the number of diabetes patients in the world has quadrupled.[2,3] According to the statistics of the International Diabetes Federation, 463 million diabetes patients will be diagnosed in 2019, and the number of diabetes patients is expected to increase to 700 million by 2045.[4,5] Chronic hyperglycemia and systemic metabolic abnormalities caused by diabetes lead to glomerulosclerosis and kidney damage, and diabetes nephropathy is the main chronic microvascular complication of diabetes.[6] Diabetes nephropathy has always been one of the main causes of chronic kidney disease and end-stage kidney disease (ESRD),[7] and diabetes nephropathy accounts for about 40% of ESRD cases.[8]

Diabetes nephropathy is a serious complication of diabetes. Abnormal changes in renal structure and function caused by diabetes microvascular disease ultimately lead to

end-stage renal injury, which is the main cause of death in diabetes patients. The main manifestations in the late stage are low glomerular filtration rate, proteinuria, and renal failure.[9,10] Diabetes nephropathy started with microalbuminuria, developed into massive albuminuria and decreased glomerular filtration rate, and finally ended with ESRD. Histologically, glomerular basement membrane thickening and mesangial dilation are the earliest lesions observed in patients with diabetes nephropathy. Afterward, there are nodular glomerulosclerosis and tubulointerstitial changes, including inflammatory cell infiltration, accumulation of activated myofibroblasts, and loss of capillary structure. Although it has been proved that many factors are involved in the pathogenesis of diabetes nephropathy, the specific molecular mechanism is complex and unclear, leading to the lack of effective treatment. Therefore, it is urgent to find new drugs to alleviate the symptoms of diabetes nephropathy and protect the renal function of diabetes patients.

Vitamin E is a lipid-soluble substance extracted from green plants, and for a long time, it was considered a reproductive-related vitamin. There are 8 isomers of vitamin E, and the isomers of tocopherol and tocotrienol have various characteristics, including effective antioxidant and anti-inflammatory properties. Vitamin E can inhibit the synthesis of diacylglycerol in microvascular endothelial cells and reduce diacylglycerol. The activity of protein kinase C pathway can improve the damage of vascular endothelial cells and microvascular function caused by hyperglycemia, and alleviate diabetic retinopathy, diabetic kidney disease and diabetic nervous system disease.[11] Vitamin E can effectively reduce urinary microalbumin, urinary albumin excretion rate and serum nitric oxide level in patients with type 2 diabetes nephropathy and can fight against renal inflammatory damage by reducing plasma high-sensitivity C-reactive protein.[12,13] In 2016, Khatami et al. conducted a randomized, double-blind, placebo-controlled clinical trial to verify that after 12 weeks of oral vitamin E intervention in diabetes patients, their urinary protein, urinary protein/creatinine ratio, serum TNF-a, matrix metalloproteinase-2 (MMP-2), MMP-9, and insulin concentration decreased significantly on average, suggesting that vitamin E has the function of protecting renal function, reducing inflammation, and oxidative stress.[14]

This study aimed to detect the role of vitamin on patients with diabetic nephropathy. Thus, we conducted a meta-analysis to examine the effect of vitamin E in patients with diabetic nephropathy.

MATERIALS AND METHODS

Selection of Studies

Study Design Type Published controlled trials on the effects of vitamin E in patients with diabetic nephropathy. And only English literature was searched. However, the animal trials were excluded.

Selection of Participants. (1) Patients with diabetic nephropathy; (2) Patients aged 18-60; (3) Patients agreed to participate in this study. All patients signed the informed consent.

Types of Interventions. The intervention group received vitamin E in the treatment of patients with diabetic nephropathy, and the control group received a placebo in the treatment of patients with diabetic nephropathy.

Types of Outcome Measures

Outcome indicators patients with diabetic nephropathy; According to research, the assessment tools for the effects of vitamin E in patients with diabetic nephropathy are: (1) HbA_{1c} (Glycated hemoglobin,%); (2) eGFR (mL/min 1.73 m^2); (3) Serum creatinine (μmol/L); (4) Urea (mmol/L); (5) Systolic BP (mmHg); (6) Diastolic BP (mmHg). The literature included in this study evaluated outcome measures using at least one of the above scales.

Search Strategy.

The computer retrieves the databases: Cochrane Library, PubMed, EMbase and Web of Science. The search term is "vitamin E" and "diabetic nephropathy". The search time was from the establishment of the library until May 2023. The specific steps of the literature search are: (1) search for relevant documents in the English databases, read the title, abstract, and Keywords to identify the search terms for this study further; (2) The English database search used "MeSH Terms" to identify the subject terms, searched using a combination of subject words and keywords.

Data Extraction and Quality Assessment

Jadad scale was used for quality of randomized controlled trials. The abstract was initially screened, and after the initial screening, the literature screening results were obtained by reading the full text, and the process was completed independently by 2 researchers. If any disagreements were between the two researchers, exchange screening results, discuss dissenting literature or consult a third researcher until the results are agreed. The information extracted from the data includes basic information of the literature, type of study, study object, sample size, intervention content, outcome measures, etc.

Statistical Analysis

This meta-analysis was conducted by using Stata software. Effects are combined: The outcome measures in this study were all measured data, and the tools used to evaluate are different. There are differences between scores; therefore, the standardized mean difference (standardized mean difference, SMD) and 95% Letters to the zone (confidence interval, CI) are used as indicators of effect. (2) Heterogeneity test: Chi-square tests are used to determine whether there is heterogeneity between studies. The included studies were considered as homogeneous and proceeded with fixed-effects model Meta analyses when $P > .1$, $I^2 < 50\%$. Heterogeneity was indicated in the included studies and analyzed heterogeneous sources if $P < .1$, $I^2 \geq 50\%$. If there is no clinical heterogeneity, a random-effects model is used, as well as meta-analyses.

Table 1. The basic characteristics of the included studies.

Study (ref.)	Sample Size (T/C)	Age(years)(T/C)	Male/ Female	T	C	Main Outcomes
2021,Yan	31/28	66±13/70±13	38/21	VE200mg bid	Pla	①②③④⑤⑥
2019, Gerald	27/27	59±10/62.8±11.6	35/19	VE200mg bid	Pla	①②③④⑤⑥
2018, Suzanne	22/23	59.9±10.24/63.3±10.42	48/18	VE200mg bid	Pla	①②③④⑤⑥
2018,Esmat	27/27	62.2±9.8/64.5±9.2	16/38	VE800mg bid	Pla	①
2016,Parisa	30/30	61.2±10.0/62.2±13.8	21/39	VE1500 IU/d	Pla	③

Abbreviations: T, trial group; C, control group; VE, Vitamin E; Pla:Placebo; ① HbA_{1c} (Glycated haemoglobin,%); ② eGFR (mL/min1.73 m^2); ③ Serum creatinine(μmol/L); ④ Urea (mmol/L); ⑤ Systolic BP (mmHg); ⑥ Diastolic BP (mmHg).

RESULTS

Search Results

Based on the search strategy, 662 references were identified. After excluding duplicate studies, 49 studies were scanned based on abstract and title. Then, 8 articles were evaluated in full text. After full-text evaluation, 3 records were excluded for the following reasons: data mismatch (n=2) and missing data (n=1). Ultimately, 5 studies[15-19] were included in this meta-analysis (Table 1). The sample sizes were more than 20. The PRISMA statement flow chart shows this process (Figure 1).

HbA_{1c}

4 studies reported the HbA_{1c} of the test group and the control group. Meta-analysis showed that the HbA_{1c} of the test group was significantly lower (SMD: -0.17; 95% Cl: -0.26,-0.07; $P < .01$, Figure 2) than the control group. A lower HbA_{1c} level means a lower average blood sugar level and a lower risk of complications developing. The funnel diagram is relatively symmetrical (Figure 3). The results of all these trials showed low heterogeneity and a sensitivity analysis was conducted (Figure 4). Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy decreases the HbA_{1c}. The Begg's Test is 0.734, and the Egger's test is 0.849, so this research results are relatively stable, and there is no obvious publication bias. There is no significant publication bias.

EGFR

3 studies reported the EGFR of the test group and the control group. Meta-analysis showed that the EGFR of the test group had no significant statistical significance (SMD: -0.90; 95% Cl: -13.30,11.49; $P = .886$, Figure 5) than the control group. Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy did not increase the EGFR. The Begg's Test is 1.000, and Egger's test is 0.291, so this research results are relatively stable and there is no obvious publication bias.

Serum creatinine

4 studies reported the Serum creatinine of the test group and the control group. Meta-analysis showed that the Serum creatinine of the test group was significantly lower (SMD: -11.20; 95% Cl: -12.89,-9.51; $P < .01$, Figure 6) than the control group. The funnel diagram is relatively symmetrical

Figure 1. Flow Chart

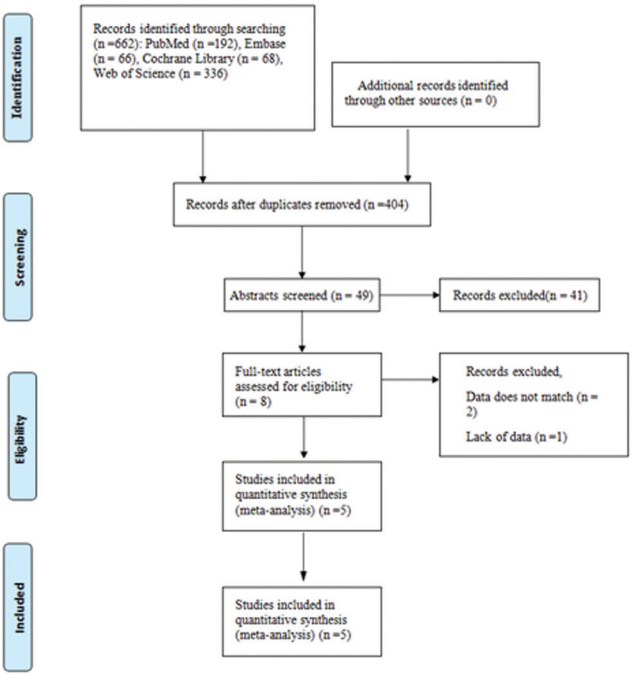


Figure 2. Forest illustration of the HbA_{1c} (Glycated hemoglobin, %).

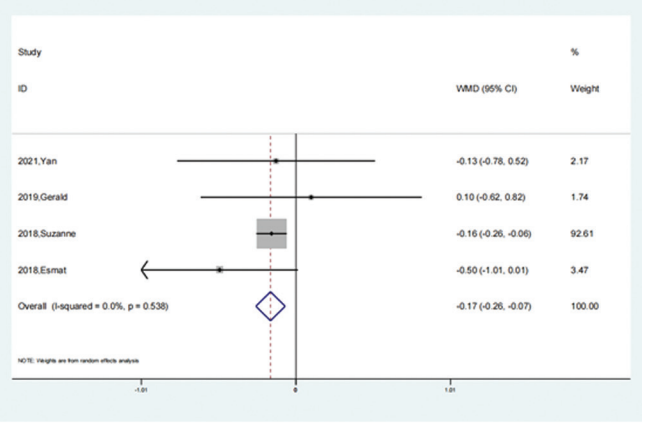


Figure 3. Funnel plot of the HbA_{1c} (Glycated hemoglobin,%).

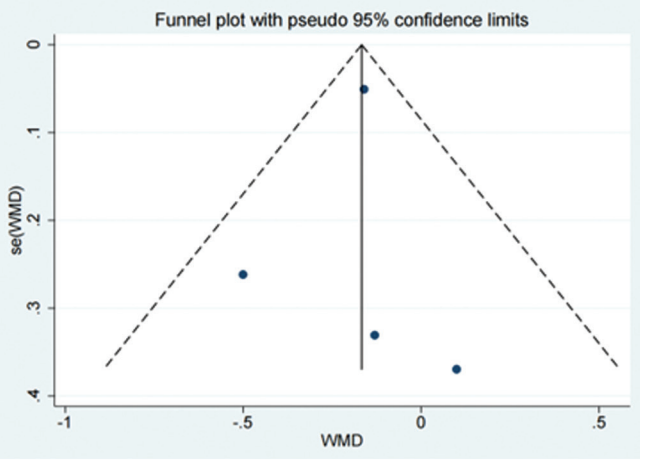


Figure 4. Sensitivity analysis of the HbA_{1c} (Glycated hemoglobin,%).

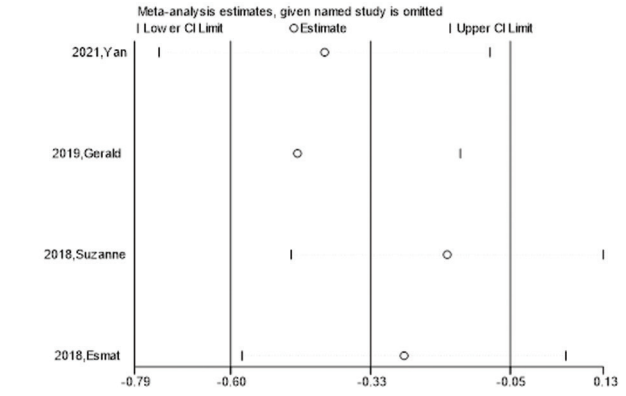


Figure 5. Forest illustration of the EGFR (mL/min 1.73 m^2).

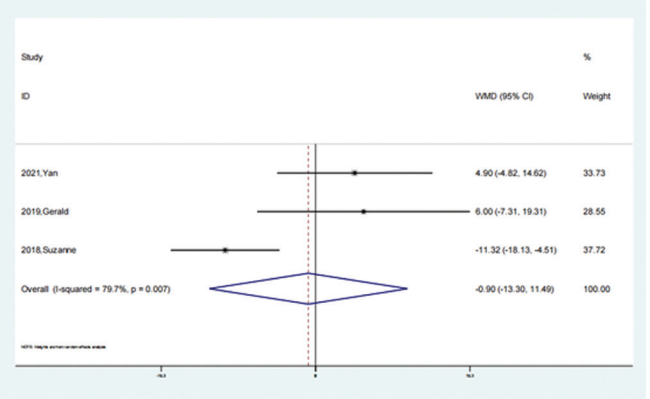


Figure 6. Forest illustration of the Serum creatinine (μmol/L).

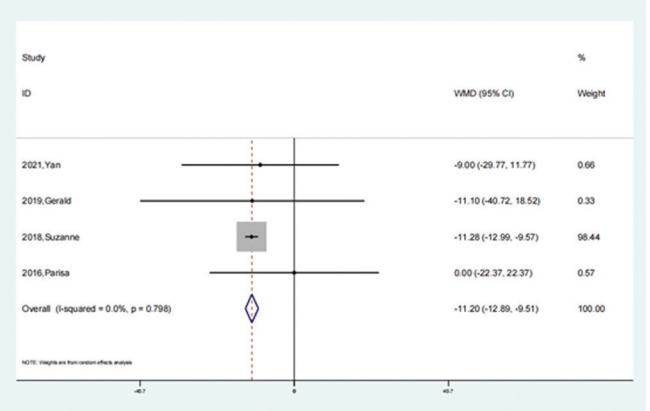


Figure 7. Funnel plot of the Serum creatinine(μmol/L).

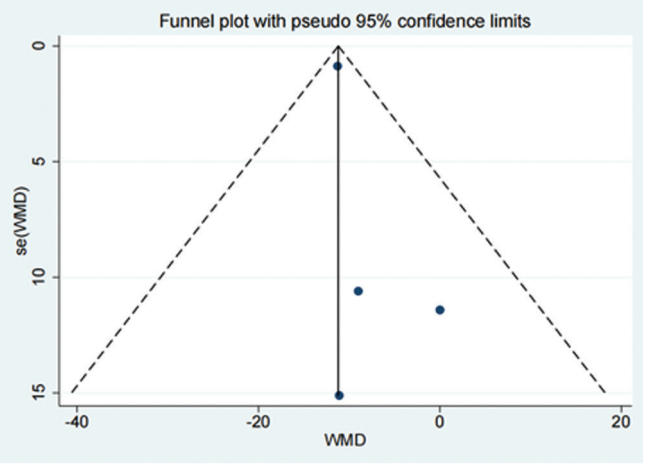


Figure 8. Sensitivity analysis of the Serum creatinine(μmol/L).

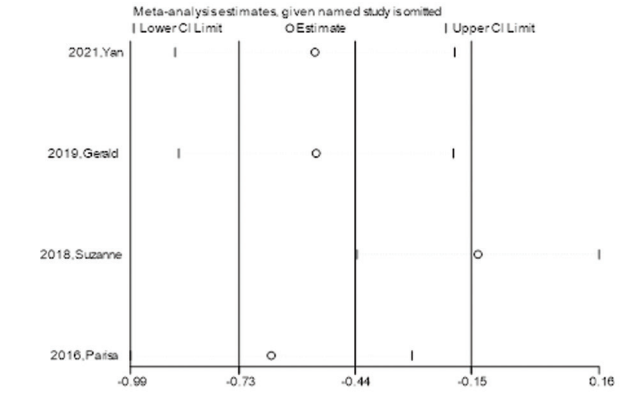
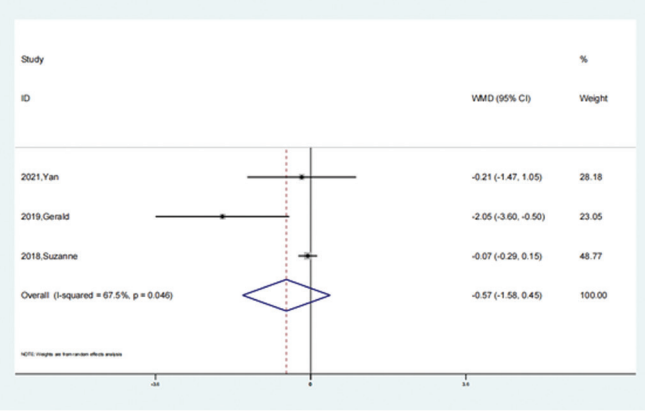


Figure 9. Forest illustration of the Urea (mmol/L).



(Figure 7). The results of all these trials showed low heterogeneity and a sensitivity analysis was conducted (Figure 8). Sensitivity analysis determines how different values of an independent variable affect a particular dependent variable under a given set of assumptions. Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy decreases the Serum creatinine. The Begg's Test is 0.734, and the Egger's test is 0.313, so this research results are relatively stable and there is no obvious publication bias.

Urea

3 studies reported the Urea of the test group and the control group. Meta-analysis showed that the urea of the test group had no significant statistical significance (SMD: -0.57; 95% Cl: -1.58,0.45; P = .275, Figure 9) compared to the control group. Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy did not decrease the EGFR. The Begg's Test is 0.296 and the Egger's test is 0.438, so this research results are relatively stable and there is no obvious publication bias.

Figure 10. Forest illustration of the Systolic BP (mmHg).

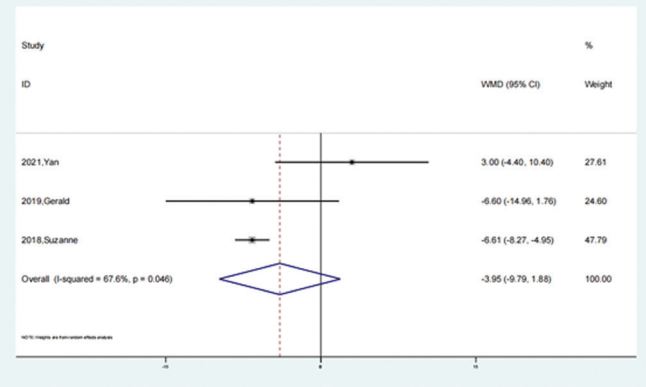
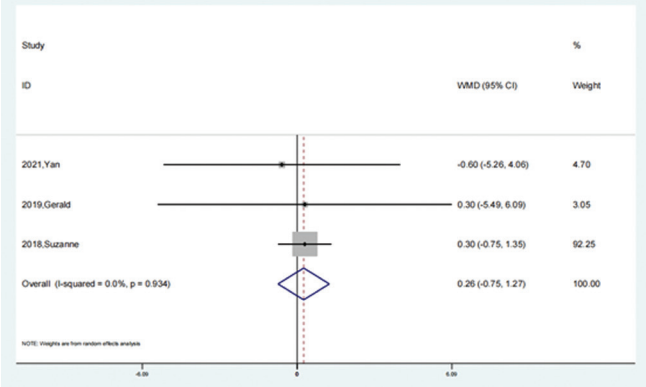


Figure 11. Forest illustration of the Diastolic BP (mmHg).



Systolic BP

Systolic pressure (high pressure): When the heart contracts, the blood from the ventricle into the side of the blood vessel wall produces pressure, when the maximum blood pressure; At this time, the pressure on the inner wall is called systolic pressure, also known as high pressure. Diastolic pressure (low pressure): is the end of the heart. In diastolic pressure, blood temporarily stops pumping into the artery, but the blood flowing into the artery depends on the elasticity and tension of the blood vessel wall, continue to flow, there is still pressure on the blood vessel wall, then the blood pressure is called diastolic pressure. Also known as low pressure. 3 studies reported the Systolic BP of the test group and the control group. Meta-analysis showed that the Systolic BP of the test group had no significant statistical significance (SMD: -3.95; 95% Cl: -9.79,1.88; $P = .184$, Figure 10) than the control group. Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy did not decrease the Systolic BP. The Begg's Test is 1.000, and the Egger's test is 0.526, so this research results are relatively stable, and there is no obvious publication bias.

Diastolic BP

3 studies reported the Diastolic BP of the test group and the control group. Meta-analysis showed that the Diastolic BP of the test group had no significant statistical significance (SMD: 0.26; 95% Cl: -0.75,1.27; $P = .617$, Figure 11) than the control group. Compared with the control group, vitamin E in the treatment of patients with diabetic nephropathy did not decrease the Diastolic BP. The Begg's Test is 1.000 and the Egger's test is 0.534, so this research results are relatively stable and there is no obvious publication bias.

DISCUSSION

Type 2 diabetes is a metabolic disease characterized by hyperglycemia and insulin resistance. Long-term poor blood sugar control can lead to serious damage to many organs, especially the nervous system and systemic vascular system, and is also the main cause of blindness, kidney failure, heart attack, stroke, and lower limb amputation. The World Health Organization believes that diabetes is one of the main causes of renal failure. In 2019, diabetes and kidney diseases caused by diabetes led to an estimated 2 million deaths. According to the data of the International diabetes Federation, diabetes nephropathy is estimated to cause 6.7 million deaths in adults under 70 years of age.[20] Diabetes nephropathy is one of the most important complications of diabetes and the main cause of ESRD. The incidence rate and mortality of DKD are rapidly increasing in the world population. Its main pathological features are glomerular hypertrophy, enlargement of the mesangial matrix, and even glomerular fibrosis and sclerosis. Microalbuminuria is the main symptom in the early clinical stage. Further development may lead to progressive kidney damage, hypertension, and edema.

For patients with chronic kidney disease, with the loss of renal function, the clearance of metabolites, toxins, and other obstacles can cause the accumulation of pro-oxidative stress molecules, and toxin accumulation further exacerbates the patient's oxidative stress state, leading to the loss of antioxidant molecules. The balance of oxidative stress state is of great significance for maintaining the body's homeostasis. When the balance between the pro-oxidative and antioxidant systems is disrupted, the pro-oxidative system becomes overactivated, the activity of antioxidant molecules is weakened, and the damage to large molecules such as proteins and lipids in the body is exacerbated. In recent years, many studies have shown that numerous antioxidants play an important role in balancing oxidative stress status in kidney disease patients, improving endothelial cell dysfunction, and reducing inflammatory markers in hemodialysis patients.[21] At present, oxidative stress is considered to be the pathogenic basis of hyperglycemia-mediated renal dysfunction, which is involved in regulating the physiological functions of the glomerulus and renal tubules. Oxidative stress-induced nephritis is an important process of the occurrence and development of renal injury in diabetes. Hyperglycemia induces the overproduction of ROS, stimulates the recruitment of inflammatory cells, and releases a large number of inflammatory factors and growth factors and transcription factors are involved in the process of diabetes nephropathy.[22]

A total of 5 literature were included in this study, including 137 patients in the experimental group and 135 patients in the control group. Meta-analysis showed that patients with diabetic nephropathy who received vitamin E had lower levels of HbA_{1c} and serum creatinine compared

with controls. Howeverm the EGFR, Urea, the Systolic BP and Diastolic BP of the test group was no significant statistical significance than the control group. This study suggested the role of vitamin E in the treatment of diabetes.

Clinical studies have found that the plasma levels of vitamin C and vitamin E in diabetes patients are reduced, and long-term supplementation of these two vitamins can reduce nephritis in diabetes patients.[23] Vitamin E can inhibit NF-κ. The activation of the B signaling pathway regulates the generation of NO2-/NO3-, increases the level of glutathione, reduces proteinuria, and alleviates proximal renal tubular injury. The results of randomized controlled studies indicate that long-term high-dose supplementation of vitamin E can significantly reduce TNF-α, The levels of MMP-2, MMP-9, malondialdehyde, and terminal glycation products inhibit oxidative stress and inflammatory responses. In addition, high-dose vitamin E supplementation can reduce the level of total cholesterol and low-density lipoprotein cholesterol in the blood, increase the total antioxidant capacity, and improve renal function damage in patients with diabetes nephropathy.[24] Recently, high-dose vitamin E supplementation has been proven to reduce renal interstitial fibrosis and apoptosis of renal tubular epithelial cells,[25] suggesting a new physiological and pathological mechanism and a possible therapeutic target of diabetes nephropathy. In addition, in the animal model of diabetes, vitamin E supplementation also seems to have a positive impact on the renal vascular system.[26] On the other hand, in high-fat diet-induced obesity models, it has been proven that supplementing vitamin E can reduce the size of adipocytes and the infiltration of adipose tissue macrophages.[27] In addition, tocopherol, in particular, seems to induce adipocyte expression, thereby activating the browning of white adipose tissue, thus further strengthening the active metabolic role of vitamin E in diabetes and diabetes nephropathy. A study reveals the mechanism of vitamin E improving renal function. It is proved in animal models that the improvement of diabetes nephropathy caused by vitamin E supplementation is mediated by activating diacylglycerol kinase, which prevents abnormal activation of protein kinase C and podocyte degeneration by reducing the circulating level of diacylglycerol.[28] Furhter studies are still needed to explore the underlying mechanism.

Limitations

The limitations of this systematic review are that only English literature was searched, and no other language literature was obtained, and there may be incomplete research inclusion and bias in selection. Also, the number of studies are not enough, which still needs further exploring. Therefore, you should be objective about some of the results of this Meta-analysis.

CONCLUSION

The results of this study suggest that vitamin E may be effective on in patients with diabetic nephropathy, as evidenced by decreasing HbA_{1c} and serum creatinine, and the above conclusions need to be verified by more high-quality studies. This will bring light for the patients and clinicians in this area.

DATA AVAILABILITY

The data could be obtained by contacting the corresponding author.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

FUNDING

This study did not receive any funding in any form.

AUTHOR CONTRIBUTIONS

Zhenjie Jin designed the study. Zhenjie Jin wrote the original draft. Wen Zhang collected raw data. Jia Sun performed statistical and bioinformatics analyses. Zhenjie Jin supervised the study.

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