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NEPHROLOGY - REVIEW

Efficacy and safety of combining pentoxifylline with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in diabetic nephropathy: a meta-analysis

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Abstract
Objective Pentoxifylline (PTF) has anti-inflammatory properties, which may be beneficial for diabetic nephropathy (DN). A meta-analysis was conducted to assess the additive effect of pentoxifylline and its safety among patients with type 2 DN under blockade of angiotensin system.
Data sources Relevant studies were searched from PubMed, CBM, EMBASE, CENTRAL and Cochrane renal group specialized register.
Selection criteria All RCTs that compared the benefits and harms of pentoxifylline and ACEI/ARB with ACEI/ARB alone for DN were included.
Data extraction and analysis Pertinent data were extracted independently by two authors. Meta-analyses were performed when more than one study provided data on a comparable outcome. Standard mean differences (SMDs) for proteinuria and albuminuria, mean differences (MDs) for systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, serum creatinine (Scr), creatinine clearance (CrCl) and urine tumor necrosis factor-alpha (UTNF-α), 95 % confidence intervals (CIs) were calculated, and heterogeneity was assessed with the I^2 test. Adverse effects were assessed using descriptive techniques.
Results Eight studies including 587 patients with a median duration of 5 months were identified. Compared with ACEI/ARB alone, the combination of PTF and ACEI/ARB significantly reduced proteinuria (SMD 0.76, 95 % CI 0.52–0.99), albuminuria (SMD 0.36, 95 % CI 0.12–0.59) and UTNF-α (MD 1.56 ng/g, 95 % CI 0.09–3.03). However, no statistically significant changes were observed for SBP, DBP, HbA1c, Scr and CrCl. The most frequent adverse effects in patients treated with PTF were gastrointestinal symptoms (28/298) and dizziness (7/298), but in most cases, these symptoms were mild, only six participants withdrew due to intractable nausea and vomiting.
Conclusions Pentoxifylline can significantly provide additive antiproteinuric effect independent from the decrease in BP or improvement in glycemic control in DN patients under blockade of angiotensin system. Further large, multicenter, high-quality studies with long duration are necessary to prove whether it really has renoprotective effects in this patient population.

Keywords Diabetic nephropathy · Pentoxifylline · Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers · Randomized controlled trails

Introduction

Diabetic nephropathy is now considered to be the major cause of end-stage renal disease (ESRD) [1]. Patients with diabetic nephropathy present much higher risk of cardiovascular events and mortality, compared with those of other causes of kidney disease [2, 3]. Albuminuria and proteinuria are the hallmarks of diabetic nephropathy, contributing to the progression of kidney disease and cardiovascular complications [4]. More urinary protein excretion causes greater renal damage, while a reduction in it by intensive therapy would have a renoprotective effect. Current therapy

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for diabetic nephropathy still primarily relies on the antiproteinuric, antihypertensive and nephroprotective effects of renin–angiotensin system (RAS) blockers [5, 6]. However, these standard therapies are insufficient to prevent progression to ESRD in a substantial number of patients with residual proteinuria (albuminuria) [7]. Dual blockade of the RAS might decrease proteinuria more effectively than single RAS blockade. However, this strategy is not recommended by the authoritative guidelines as no additional efficacy in terms of renal function has been demonstrated and the incidence and severity of adverse effects (such as hyperkalemia and AKI) are increased [5, 6, 8]. The ALTITUDE and VA NEPHRON-D RCTs showed no beneficial effects of dual versus single RAS blockade on renal function, and both studies were stopped prematurely for safety reasons [9, 10]. Despite great advances in the knowledge of molecular and cell signaling pathways involved in kidney injury, few new drugs are coming into the market to treat diabetic nephropathy due to the lack of effects or serious safety concerns.

Pentoxifylline (PTF) is a methylxanthine phosphodiesterase inhibitor with significant hemorheological effects, clinically used to treat patients with occlusive peripheral arterial disorders for more than 40 years [11]. PTF also has anti-inflammatory, antifibrotic and antiproliferative actions in animal models of DN [12]. Inflammation is recognized as a key contributor in the pathogenesis and progression of DN [13]. Phosphodiesterase inactivates the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), inactivates protein kinase A (PKA) and enhances leukotriene and TNF synthesis, leading to inflammation. Urinary TNF-α level was an independent predictor of urinary albumin excretion in individuals with type 2 diabetes [14]. As a non-selective phosphodiesterase inhibitor, PTF can reduce inflammatory factors including IL-1, IL-6 and TNF-α which play important roles in the pathogenesis and progression of diabetic nephropathy [15]. Clinical studies in patients with DN have also shown that pentoxifylline reduces inflammatory effects and attenuates proteinuria [14, 16].

To date, clinical trials evaluating pentoxifylline in patients with DN had small sample sizes or were single-center designs. Though McCormick et al. and Shan et al. conducted a meta-analysis, respectively, which assessed the effect of pentoxifylline on proteinuria in patients with DN, but the two analyses were limited to articles published before 2010. In addition, they did not specially detect the additive effects of PTF based on RAS blockers [17, 18]. Therefore, we conducted a meta-analysis of appropriate published RCTs to determine the efficacy and safety of pentoxifylline plus RAS blockers in diabetic nephropathy.

Methods

Search strategy and study selection

A computerized search of the PubMed, CBM, EMBASE, CENTRAL and Cochrane renal group specialized register was independently undertaken by two authors to identify potentially eligible RCTs. The search was not limited to English language or publication type. All searches were up to date as of December 2014. The following subject heading terms or key words were used in our search: ("diabetes mellitus or diabetic nephropathies or diabetic kidney disease or diabetic or diabetes") and ("pentoxifylline or pentoxifylline or oxpentifylline or torental or trental or agapurin or bl-191"). The reference lists from included RCTs, relevant systematic reviews and narrative reviews identified by electronic databases were hand searched to identify other potentially eligible articles. Studies were included in the meta-analysis if the following criteria were met: Randomized controlled trials that compared the benefits and harms of oral pentoxifylline plus ACEI/ARB with ACEI/ARB alone for patients of DN defined as albuminuria with greater than 30 mg/d, or estimated glomerular filtration rate <60 mL/min/1.73 m^2; reporting at least one of the following outcomes: proteinuria, albuminuria, serum creatinine level, creatinine clearance or estimate of glomerular filtration rate. Trials that included subjects with renal replacement therapy or kidney damage relating to diseases other than diabetes were excluded. There was no restriction on sample size or intervention duration. Two investigators independently searched and assessed all citations for potentially eligible studies. Titles and abstracts from the electronic search were reviewed. After the initial review of the abstracts, the relevant studies were identified and a detailed evaluation of the full text was done. Disagreements or uncertainties were adjudicated by consensus or by consulting a third reviewer. In the case of multiple reports of with the same or overlapping data published by the same authors, we combined the informative data and retained only the complete article to avoid duplication of information.

Data extraction and quality scoring

Data extraction was performed independently by two authors using standardized data extraction forms. The following information was extracted from the included studies: first author's name and publication year, sample size, trial design, demographic data (DM type and duration, body mass index, mean age, gender and location), daily dosage of PTF and control therapy, length of follow-up, dropouts and adverse events. We were interested in the following outcomes, including information on baseline and

final concentrations (or net changes) of proteinuria, albuminuria, Scr, r, SBP, DBP, HbA1c and UTNF-α. These values were captured as the mean change from baseline to follow-up (with mean ± SD). The mean changes were calculated by subtracting the final values from the baseline values. Additionally, the standard deviations of the mean changes [SD(C)] were calculated according to the following formula:

$$\mathrm{SD}(C) = \sqrt{\mathrm{SD}(B)^2 + \mathrm{SD}(F)^2 - (2 \times R \times \mathrm{SD}(B) \times \mathrm{SD}(F))}$$

We assumed a pre–post study correlation R of 0.5 to get an estimate of the mean change in SD. This allowed for the calculation of the mean effect size between pre–post change for PTF and control. We also conducted a sensitivity analysis assuming 0.25 and 0.75 as correlation between baseline and final values. Results did not change, and thus, data using a correlation of 0.5 are presented in this analysis. The quality of each study was evaluated using validated Jadad 5-point scale [19].

Studies with scores of 4 or higher are considered to be ones of high quality, and Jadad score not more than two indicates the low quality.

Data analysis and synthesis

According to the guideline in the Cochrane reviewers' handbook, all analyses were performed with RevMan5.0 software. Due to different scales used in studies or the wide difference of the mean, standardized mean differences (SMDs) with 95 % CIs were calculated for proteinuria and albuminuria. For Scr, CrCl, SBP, DBP, HbA1c and UTNF-α, mean differences (MDs) with 95 % CIs were counted. Between-study heterogeneity was assessed using the Chi-square test. Studies with an I^2 statistic of 25–50 % were considered to have low heterogeneity, an I^2 statistic of 50–75 % were considered to have moderate heterogeneity, and an I^2 statistic of >75 % were considered to have a high heterogeneity [20]. Fixed-effect analysis was used when $I^2 \leq 50$ %. Otherwise, the random-effect model was employed. Statistical significance was set at a two-tailed level of 0.05 for hypothesis testing. Adverse effects were assessed using descriptive techniques. Funnel plots and subgroup analyses could not be conducted because of the few included studies.

Results

Characteristics of included studies

As outlined in Fig. 1, the search strategy generated 358 studies. After applying inclusion and exclusion criteria, eight

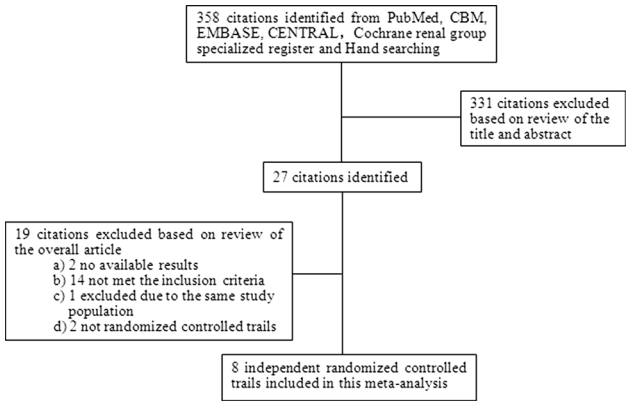

Fig. 1 Flowchart of search

randomized controlled trials with a total of 587 patients were included in this meta-analysis [21–28]. The characteristics and details of the included studies are summarized in Tables 1, 2 and 3. Studies generally were of small sample size, and the median number of participants was 58. Only two trials had 100 or more than 100 participants. All patients had been diagnosed as type 2 DN. The baseline characteristics of the patients were balanced between the PTF and control group. In five trials, pentoxifylline dose was 1200 mg/d; in one trial, dose was 600 mg/d; and in two trials, dose was 400 mg/d. The duration of therapy ranged from 21 days to 2 years, with a median of 5 months. The primary outcome of proteinuria was reported in five studies, and the other three trails reported results of albuminuria. Jadad scores were low, with a median score of 3 (range 2–4). The investigated populations of each study were too small to turn out significant results in these variables, but when they were assessed together in a meta-analysis, sufficient numbers of patients were available for a more reliable analysis.

Quantitative data synthesis

(1) Proteinuria, albuminuria and UTNF-α

The pooled SMDs for proteinuria and albuminuria from the fixed-effect model are shown in Fig. 2. Five trials reported on the primary outcome of proteinuria. The meta-analysis suggested that proteinuria levels were decreased significantly in the PTF plus ACEI/ARB group compared with that of the control group (SMD0.76; 95 % CI 0.52–0.99, $p < 0.001$). The test for heterogeneity was low ($I^2 = 24$ %). The effect of PTF on albuminuria was assessed in three studies with 280 DN patients. Compared with ACEI/ARB alone, PTF plus ACEI/ARB could lead to a greater reduction in albuminuria (SMD0.36; 95 % CI 0.12–0.59, $p = 0.004$; $I^2 = 0$ %). Two studies reported UTNF-α (Fig. 3). The combination of PTF and ACEI/ARB could

Table 1 Characteristics of the included randomized controlled trials

References	Sample size (*n*)	Country	Double blind	Duration	Main intervention (PTF/control, daily dosage)	Withdrawals (intervention/control)
Harmankaya et al. [21]	50	Turkey	No	9 months	PTF600 mg and lisinopril 10 mg; lisinopril 10 mg	0/25, 0/25
Navarro et al. [22]	45	Spain	No	4 months	PTF 1200 mg and ACEI or ARB; ACEI or ARB	0/30, 0/15
Navarro et al. [23]	61	Spain	No	4 months	PTF 1200 mg and ARB; ARB	0/30, 0/31
Roozbeh et al. [24]	74	Iran	No	6 months	PTF1200 mg and captopril 75 mg; captopril 75 mg	2/37, 2/37
Oliaei et al. [25]	56	Iran	No	3 months	PTF 1200 mg and ACEI or ARB; ACEI or ARB	0/28, 0/28
Jin-Lei et al. [26]	32	China	No	21 days	PTF400 mg and valsartan 80 mg; valsartan 80 mg	0/16, 0/16
Ghorbani et al. [27]	100	Iran	Yes	6 months	PTF400 mg and losartan 50 mg and enalapril 15 mg; losartan 50 mg and enalapril 15 mg	6/50, 0/50
Navarro et al. [28]	169	Spain	No	2 years	PTF 1200 mg and ACEI or ARB; ACEI or ARB	4/82, 5/87

PTF pentoxifylline, *ARB* angiotensin receptor blockers, *ACEI* angiotensin-converting enzyme inhibitor

Table 2 Characteristics of the included randomized controlled trials (intervention/control group)

References	DM type and duration (years)	Male/female	Mean age (years)	BMI (Kg/m^2)	Primary outcome	Jadad score
Harmankaya et al. [21]	Type 2, 12.9/12.7	31/19	58.3/58.7	31.9/31.7	Scr, UAE, SBP, DBP, HbA1c	2
Navarro et al. [22]	Type 2, 12/11	24/21	63/66	UN	Scr, proteinuria, SBP, DBP, HbA1c	3
Navarro et al. [23]	Type 2, 13.1/12.5	31/30	58.6/58.8	30.4/29.3	Scr, UAE, SBP, DBP, HbA1c, UTNF-α	3
Roozbeh et al. [24]	Type 2, 4.6/6.3	33/27	53.9/53.5	UN	Scr, proteinuria, SBP, DBP, HbA1c, Ccr	3
Oliaei et al. [25]	Type 2, 11.9/14.0	18/38	55.3/57.6	UN	Proteinuria, Ccr	2
Jin-Lei et al. [26]	Type 2, 11/10	16/16	55.4/57.4	22/21.3	Scr, proteinuria, SBP, DBP, Ccr	2
Ghorbani et al. [27]	Type 2, 8.9/8.5	54/46	56/58	32.1/31.8	Proteinuria, Ccr, Scr, SBP, DBP, HbA1c,	4
Navarro et al. [28]	Type 2, 15.3/14.8	91/78	70.2/69.5	29.4/28.9	eGFR, UAE, SBP, DBP, HbA1c, UTNF-α	3

DM diabetes mellitus, *UAE* urinary albumin excretion, *Scr* serum creatinine, *Ccr* creatinine clearance, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *UTNF-α* urine tumor necrosis factor-alpha, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *UN* unknown

significantly reduce urine TNF-α level (WMD 1.56 ng/g; 95 % CI 0.09–3.03, $p = 0.04$; $I^2 = 23$ %).

(2) Kidney function, blood pressure and HbA1c

Six trials reported serum creatinine levels. Pooled analysis showed no significant effect of pentoxifylline on change in serum creatinine levels (WDM, −0.04 mg/dL; 95 % CI −0.15 to 0.06; $p = 0.42$). The test for heterogeneity was high ($I^2 = 52$ %). Four trials reported creatinine clearance, and PTF plus ACEI/ARB treatment did not significantly change the creatinine clearance level compared with that of control group (WDM, −0.65 mL/min; 95 % CI −4.21 to 2.91; $p = 0.72$; $I^2 = 0$ %). Seven trials reported blood pressure. There were no significant differences in either systolic (WDM, 0.3 mmHg; 95 % CI −2.3 to 2.9; $p = 0.82$; $I^2 = 81$ %) or diastolic blood pressure (WDM 0.8 mmHg; 95 % CI −0.06 to 1.66; $p = 0.72$; $I^2 = 48$ %) between two groups. Six trials reported HbA1c. No significant change was observed in the PTF group compared with that of the control group (WDM 0.09 %; 95 % CI −0.04 to 0.21; $p = 0.16$; $I^2 = 0$ %). These detailed results are shown in Fig. 3.

Adverse effects

The most frequent adverse effects in patients treated with PTF were gastrointestinal symptoms (28/298) and dizziness (7/298), but in most cases, these symptoms were mild, only six participants withdrew due to intractable nausea and vomiting. According to Roozbeh et al. [24], four participants were excluded: One person from each group was excluded due to uncontrolled hypertension, one from control group due to hyperkalemia as a result of captopril

Table 3 Baseline characteristics of participants in the RCTs (intervention/control group)

References	Albuminemia (mg/d)	Proteinuria (g/d)	CrCl (mL/min) or eGFR (mL/min per 1.73 m^2)	Blood pressure (mmHg)	UTNF-α (ng/g)	HbA1c (%)
Harmankaya et al. [21]	219/228	Not reported	Not reported	148/149 83/83	Not reported	7.9/7.7
Navarro et al. [22]	Not reported	0.92/0.79	Not reported	137/138 78/80	Not reported	7.6/7.5
Navarro et al. [23]	900/920	Not reported	Not reported	134.4/132.1 83.3/81.5	15/14	8.02/8.07
Roozbeh et al. [24]	Not reported	2.95/2.79	105.4/103.6	129/128 78/79	Not reported	7.06/6.64
Oliaei et al. [25]	Not reported	1.65/1.1	80.18/80.9	Not reported	Not reported	Not reported
Jin-Lei et al. [26]	Not reported	3.4/3.2	49.1/47.3	143.3/141.8 99.8/101.2	Not reported	Not reported
Ghorbani et al. [27]	Not reported	6.2/5.2 (g/L)	83.76/84.48	122.2/124.4 72.3/74.6	Not reported	8.05/8.03
Navarro et al. [28]	1100/1000	Not reported	37.1/37.6	142.2/141.8 86.5/86.4	16/16	7.3/7.2

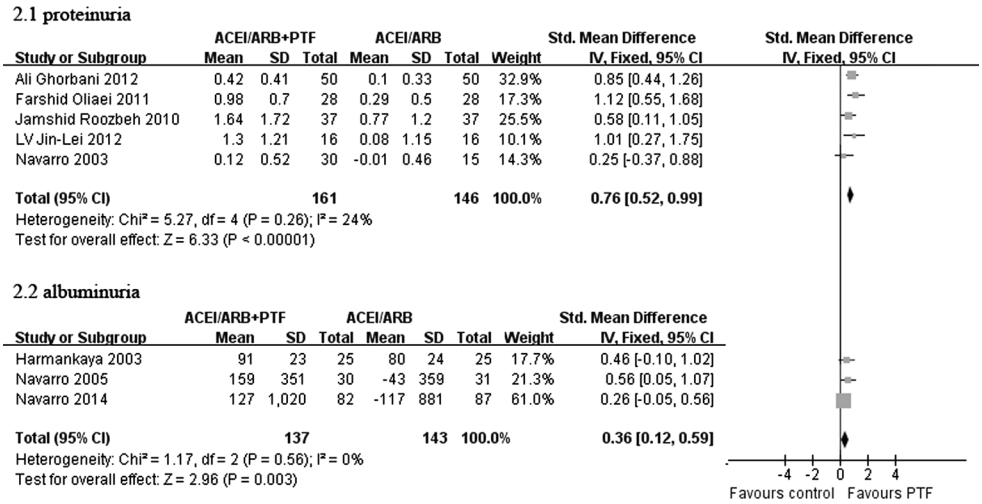

Fig. 2 Forest plots for urinary protein excretion

use and one in PTF group due to nausea and vomiting as a result of PTF use. In one trail, six patients from PTX group were excluded because of chest pain and dyspnea in one, retinal hemorrhage in another and intractable nausea and vomiting in four patients [27]. In another study, five patients initiated dialysis during the study (three in the control group and two in the PTF group); one patient in each group died; one participant in PTF group withdrew because of intolerant gastrointestinal symptom [28].

Discussion

This meta-analysis included a total of eight studies with 587 patients focusing on the efficacy and safety of oral pentoxifylline plus ACEI/ARB for diabetic nephropathy. Compared with ACEI/ARB alone, the addition of PTF causes a significant reduction in urinary protein excretion and this effect seems to be associated with a reduction in urinary TNF-α excretion, yet independent from blood pressure and glycemic control. In this review, pooled analysis did not show significant effect of pentoxifylline plus ACEI/ARB on change in serum creatinine or creatinine clearance levels. This lack of benefit for them may be related to the shorter observation time, with median duration of 5 months in the included studies. Several clinical trials with longer follow-up indeed found that PTF could reduce the rate of progression of renal disease, and the between-group difference in the reduction of eGFR reached statistical significance only after a year of administration [28–30]. Recently, the PREDIAN trial found that treatment with PTF for 24 months led to a significant mean difference of

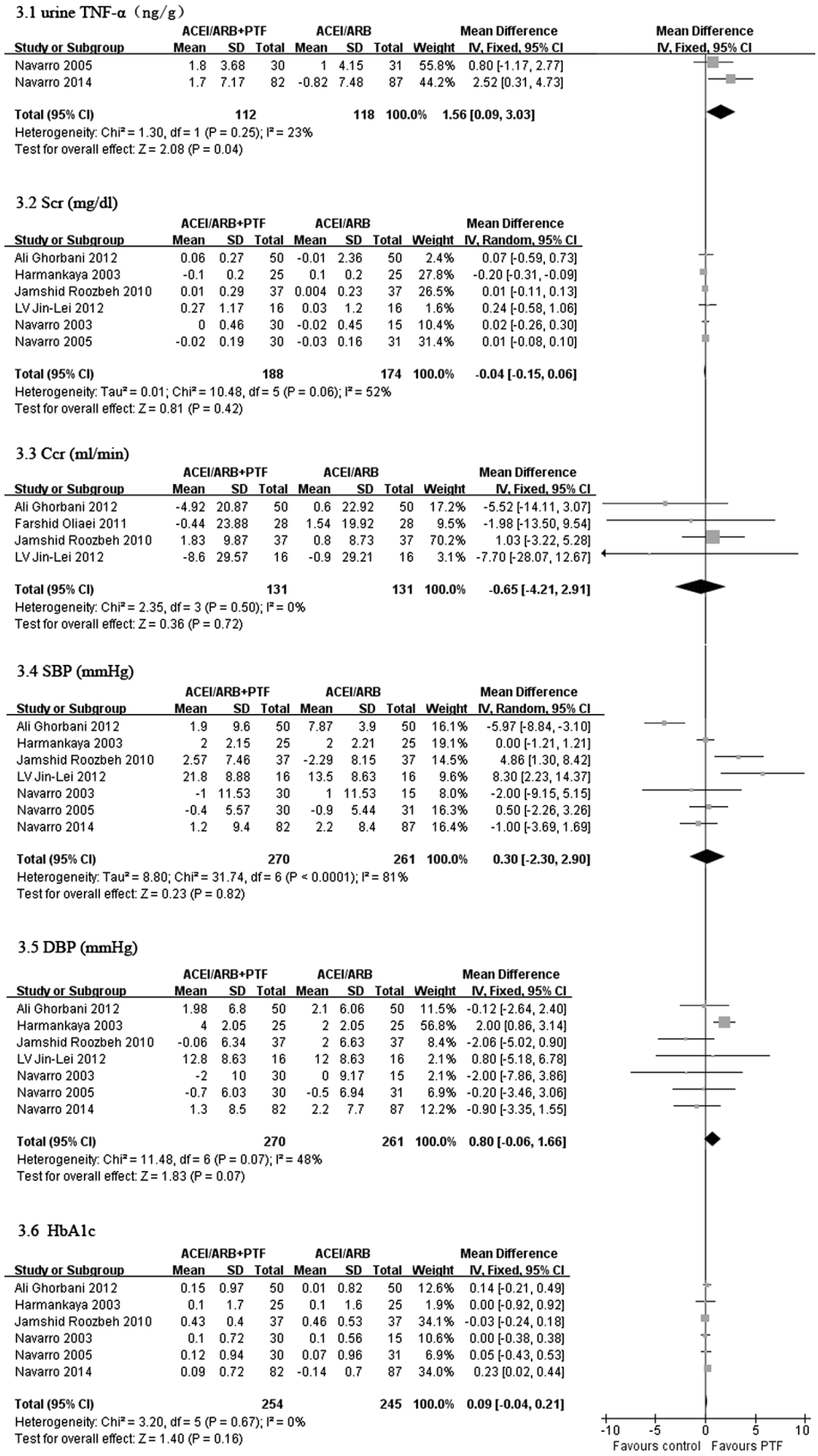

Fig. 3 Forest plots for urine TNF-α, kidney function, blood pressure and HbAlc

4.3 mL/min per 1.73 m^2 in the reduction of eGFR among patients with type 2 diabetes who had stages 3–4 CKD and were receiving the maximum recommended dosage of ACEIs or ARBs. Moreover, the proportion of patients with a rate of eGFR decline greater than the median (0.16 mL/min/1.73 m^2 per month) was significantly lower in the PTF group (33.3 %) than in the control group (68.2 %, $p < 0.001$) [28]. Regarding the antiproteinuric effects of PTF, the onset time in different trails is inconsistent, from the earliest 21 days to the latest 6 months after administering the drug [24, 26, 28]. The definitive onset time and effect degree of PTF on diabetic nephropathy should be answered by large-scale and multicenter studies. The adverse effects were consistent with the known safety profile of PTF obtained from a wide clinical experience for more than 40 years in patients with peripheral vascular disease, and transient digestive symptoms, dizziness and headache were the most common adverse reactions in patients of diabetic nephropathy.

The combined therapy of PTF and ACEI/ARB may offer greater antiproteinuric and renoprotective actions than ACEI/ARB alone. In addition to its rheologic effect with reduction in blood viscosity and a subsequent decrease in glomerular hydraulic pressure, preclinical researches indicate that PTF treatment can also lead to improvements in markers of inflammation, oxidative stress, cell proliferation and fibrosis [12, 31]. Although exact mechanisms of the renoprotective effect of PTF for diabetic nephropathy are not clearly understood, the most likely explanation may involve its ability to inhibit the production of proinflammatory cytokines, such as monocyte chemoattractant protein 1(MCP-1), IL-1, IL-6 and TNF-α [15, 32]. Diabetic nephropathy is a primary inflammatory state, and existing pieces of evidence suggest that proinflammatory cytokines may have a pathogenic role in increasing glomerular permeability to serum protein [33]. Among them, especially TNF-α has been shown to be cytotoxic to glomerular mesangial and epithelial cells, which causes significant glomerular injury [34]. PTF administration has been shown to inhibit the production of TNF-α in animal models and humans by inhibiting the transcription and translation of TNF-alpha gene [35]. In the PREDIAN trial and other clinical studies, the change in urinary TNF-α levels correlated directly with change in UAE and inversely with change in eGFR. There was no significant correlation between the serum and urinary concentrations of TNF-α, which suggests PTF might modulate intrarenal TNF production [12, 23, 28].

Strengths of our meta-analysis include composing of RCTs and selection of a homogenous type 2 diabetes population. The I^2 statistics for proteinuria and albuminuria display an acceptable risk of between-study heterogeneity, and this combined with narrow confidence intervals suggests that our findings are valid. Our study also has some potential limitations. Firstly, there was a marked absence of blinding or placebo use reported in the included studies, which often favors the treatment group. Secondly, there was a notable absence of data on clinically hard outcomes such as ESRD incidence, cardiovascular events and mortality at long-term follow-up. The included studies focused mainly on albuminuria, proteinuria, Scr, CrCl and blood pressure, which acted as surrogate endpoints. Thirdly, funnel plots for publication bias could not be made because of the limited numbers of studies for each outcome. Last but not least, due to the limited number of studies of PTF for the specific outcomes, subgroup analyses could not be conducted to compare dose, treatment duration, type of RAS blockers and baseline proteinuria level for each outcome.

Conclusions

Combining an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and pentoxifylline could lead to a greater reduction in proteinuria and albuminuria in patients of DN independent of the decrease in BP or improvement in glycemic control. Further large, multicenter, high-quality studies with long duration are necessary to prove whether it can cause a reduction in hard endpoints, such as death or the need for dialysis.

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Conflict of interest None.

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