



Effect of probucol on insulin resistance in patients with non-diabetic chronic kidney disease

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Abstract

Background Insulin resistance (IR) is present at all stages of chronic kidney disease (CKD) and is associated with CKD progression. Probucol can improve the prognosis of IR in diabetes mellitus (DM) patients. This study aimed to observe the effect of probucol on IR and kidney protection in non-diabetic CKD patients. **Methods** This was an open-label, non-placebo-controlled, randomized study. A total of 59 patients were randomized to the probucol group (0.5 g, twice daily) or the control group using a 1: 1 treatment ratio. IR was determined using a homeostatic model assessment-IR (HOMA-IR) index. An Excel database was established to analyze follow-up data at weeks 0, 12, and 24. The primary outcome of interest was changes in the HOMA-IR, and the secondary outcomes of interest were changes in the estimated glomerular filtration rate (eGFR), body mass index (BMI), cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and 24-h urinary protein. **Results** The HOMA-IR index of the probucol group after 24 weeks was significantly decreased ($P < 0.001$) compared to the value before treatment (average decrease: 1.45; range: -2.90 to -0.43). The HOMA-IR index in the control group increased (average increase: 0.54; range: -0.38 to 1.87). For the secondary outcomes of interest, the changes between these two groups also exhibited significant differences in eGFR ($P = 0.041$), cholesterol ($P = 0.001$), fasting insulin ($P < 0.001$), and fasting C-peptide ($P = 0.001$). **Conclusions** Compared to angiotensin receptor blockers alone, the combination with probucol ameliorates IR in non-diabetic CKD patients and delays disease progression.

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Keywords: Chronic kidney disease; Insulin resistance; Probucol

1 Introduction

Studies on the progression of abnormalities associated with metabolic syndrome and chronic kidney disease (CKD) are receiving substantial attention. Two prospective studies confirmed that metabolic syndrome conditions are risk factors for the progression of CKD in non-diabetic adult/elderly patients.^[1,2] Insulin resistance (IR) is considered a core issue of metabolic syndrome. IR refers to the reduction in the sensitivity of insulin target organs to the function of insulin; that is, IR is a status in which a normal dose of insulin produces a lower-than-normal biological effect. Homeostatic model assessment (HOMA) is the most commonly used method for evaluating IR (HOMA-IR). It has been

reported that IR is universally present at each stage of CKD and is associated with micro-inflammatory responses, oxidative stress, hyperlipidemia, vitamin D deficiency, and metabolic acidosis.^[3] Our previous studies also showed that IR was one of the risk factors associated with IgA nephropathy.^[4] Therefore, whether the progression of CKD could be delayed by improving the outcome/course/prognosis of IR is worth further study.

The current clinical treatments of IR include antidiabetic drugs, such as thiazolidinediones and metformin,^[5,6] antioxidants, such as vitamin A and E,^[7] renin-angiotensin system (RAS) blockers, such as telmisartan and irbesarta,^[8] and methods that emphasize exercise and a balanced diet.^[9] However, these reports mainly involved IR treatment in patients with diabetes mellitus (DM); currently, clinical studies on IR in CKD patients are lacking.

Probucol, or 4,4'-[(1-methylethylidene)bis(thio)]bis[2,6-bis(1,1-dimethylethyl)phenol], inhibits low-density lipoprotein (LDL) synthesis and promotes its degradation to effectively reduce the level of low-density lipoprotein cholesterol

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(LDL-C). Therefore, it is usually classified as a lipid-lowering drug. It is generally considered that upon lowering cholesterol, this drug also reduces high-density lipoprotein (HDL) levels; thus, probucol is usually used to treat atherosclerosis. Because of its antioxidant functions, studies have also shown that probucol reduces inflammatory responses and that its clinical usage was essentially safe.^[10] The literature reports that probucol ameliorates IR^[11] and exhibits a certain therapeutic effect on proteinuria in diabetic kidney diseases,^[12] but the mechanism behind this effect remains unclear. Our previous studies showed that probucol improves urea-induced IR in muscle cells, suggesting that it might be effective for IR in CKD patients.

Currently, certain RAS blockers, such as telmisartan, irbesartan, and valsartan, have been shown to reduce the HOMA-IR index, which might result from their additional ability to activate peroxisome proliferator-activated receptor-gamma (PPAR- γ).^[8,13] This clinical study used angiotensin receptor blockers (ARBs) as the baseline medication to study the effects of adding probucol to the protocol for IR and CKD progression.

We speculated that probucol helps reverse IR in patients with non-diabetic CKD. It has been reported that IR increases the incidence of CKD in non-diabetic patients.^[14] Therefore, we also proposed that interventions in IR might help to delay CKD progression. This study performed a controlled investigation of the effect of probucol on IR in CKD patients with a baseline of renin-angiotensin system (RAS) inhibitor treatment and further examined its kidney protective effects.

2 Methods

2.1 Subjects

The study subjects were CKD patients who were hospitalized in the Department of Nephrology of the Chinese PLA General Hospital from February 2013 to February 2014. The inclusion criteria were as follows: (1) confirmed CKD based on Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines; (2) age between 18 and 70 years old; (3) HOMA-IR index > 2; (4) estimated glomerular filtration rate (eGFR) \geq 30 mL/min per 1.73 m² and no renal replacement therapy; (5) body mass index (BMI) \leq 32 kg/m²; and (6) regular ARB treatment for at least three months without adjusting the dose and type during the experimental period.

The exclusion criteria were as follows: (1) confirmed type 2 DM, or a family history of type 2 DM; (2) treatment with corticosteroids or immunosuppressants; (3) the use of drugs that could improve IR, such as statins; and (4) com-

plications that might affect the study results, such as chronic liver disease, myocardial infarction, prolonged Q-T interval suggested by electrocardiogram findings, pancreatic diseases, and mental disorders. This study was approved by the Ethics Committee of the Chinese PLA General Hospital, and all of the patients signed informed consent forms before enrollment.

2.2 Study protocol

A statistician obtained a randomization sequence using computers and placed it in a non-transparent envelope. The randomization was completed by persons who were not related to the study. The detailed data of patients from February 2013 to February 2014 who met the inclusion and exclusion criteria were recorded. The experimental group that did not have clear drug contraindications was treated with probucol; the dosage of 0.5 g was administered twice daily. Some patients were told to submit their medication records during follow-up visits to evaluate treatment compliance. Physical examination results, such as height, body weight, and blood pressure, were recorded. Blood indicators (fasting insulin, fasting C-peptide, fasting glucose, creatinine, total cholesterol, triglycerides, HDL, and LDL) and a urine indicator (quantitation of 24-h urine protein) were examined, and an electrocardiogram was performed. Follow-up was conducted for 24 weeks, and an Excel database was established. If the control of blood pressure in the patients was not excellent during follow-up, non-RAS antihypertensive drugs were used to control blood pressure to within the ideal range.

2.3 The primary and the second outcome of interest

The primary outcome of interest was the HOMA-IR index, which was calculated using the following method: $\text{HOMA-IR} = \text{FIN} * \text{FGLU} / 22.5$ (FIN: fasting insulin; FGLU: fasting glucose). An HOMA-IR > 2 was used as an inclusion criterion, and these patients were considered to have IR.^[4] The secondary outcomes of interest were eGFR, creatinine clearance rate (CCR), BMI, cholesterol, triglycerides, HDL, LDL, and 24-h urine protein. The calculation of eGFR used the simplified Modification of Diet in Renal Disease (MDRD) formula recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI). BMI was calculated as body weight (kg)/height (m²).

2.4 Statistical analysis

All the patients who met the inclusion and exclusion criteria were used for the statistical analysis. A total of 59 patients (29 in the probucol group and 30 in the control group) received follow-up at 12 and 24 weeks after entering the

study. Continuous variables were presented as the mean \pm SD or the median (quartile). Categorical variables were described using frequency and percentage. For the primary outcome of interest, a comparison of the changes in HOMA-IR between the baseline and after 24 weeks in the two groups was performed. The absolute change in the HOMA-IR index was the difference between the HOMA-IR value at 24 weeks and the HOMA-IR value at baseline. The percentage change in the HOMA-IR index was calculated as the absolute change divided by the baseline value. An examination of the significance of HOMA-IR changes between the two groups was performed using the Mann-Whitney test. The 1/SQRT (HOMA-IR) formula was used for normal transformations, and the repeated measurement method was used to analyze the features of the HOMA-IR index changes at different time points. The changes in other continuous effective variables were analyzed using the above methods. After calculation, if the change in the HOMA-IR index from baseline to the final measurement was 0.5 ± 0.5 , 80% was selected as the power of the two-tailed test with a sample size of 64 people in the two groups during the treatment. The statistical analyses were performed using SPSS 17.0 software. The differences were significant when $P < 0.05$.

3 Results

3.1 General data and baseline measurement results

During the study period, 153 cases met the criteria of IR increase, of which 42 cases using corticosteroids or immunosuppressants, 35 cases with DM, and 17 cases using lipid-lowering drugs were excluded. A total of 59 cases were enrolled. These cases were divided into the probucol treatment group (29 cases) and the control group (30 cases). These 59 cases were followed for 24 weeks (Figure 1).

Table 1 shows the baseline results for these two groups. The demographic data, blood pressure, blood glucose, blood lipids, HOMA-IR index, renal function, 24-h urine protein, CKD staging, and ARB types did not exhibit significant differences and did exhibit comparability ($P > 0.05$) between the two groups. During the study, three patients received hemodialysis treatment (two in the treatment group and one in the control group), and these patients were all included in the final analysis.

3.2 The changes in the HOMA-IR index and the secondary indicators of interest

Table 2 shows the changes in indicators and their differences in the probucol group and the control group after 24

weeks. After 24 weeks, the HOMA-IR index in the probucol group decreased significantly compared to the value before treatment (average decrease: 1.45; range: -2.90 to -0.43), whereas the HOMA-IR index in the control group increased (average increase: 0.54; range: -0.38 to 1.87); the difference between these two groups was statistically significant ($P < 0.001$).

Among the secondary outcomes of interest, the changes in eGFR in the probucol group (average increase: 3.12; actual: -3.20 to 10.47) and in the control group (average decrease: 0.87; actual: -15.82 to 6.15) exhibited statistical significance ($P = 0.041$). The changes in cholesterol ($P = 0.001$), fasting insulin ($P < 0.001$), and fasting C-peptide ($P = 0.001$) in these two groups also exhibited statistical significance. However, the changes in indicators, such as BMI ($P = 0.690$), 24-h urine protein ($P = 0.070$), triglycerides ($P = 0.481$), and uric acid ($P = 0.327$), from the baseline to 24 weeks of follow-up in the two groups did not exhibit significant differences.

3.3 Repeated measurement analysis of the HOMA-IR index

Table 3 shows the results of the repeated measurement analyses of the major indicator (HOMA-IR index). The results suggested that the time effect ($P = 0.003$) and the interactive effect between time and group ($P < 0.001$) was significant, whereas the group effect did not exhibit a significant difference ($P = 0.248$).

3.4 Changes in the HOMA-IR index

Table 4 shows a further analysis of the changes in the

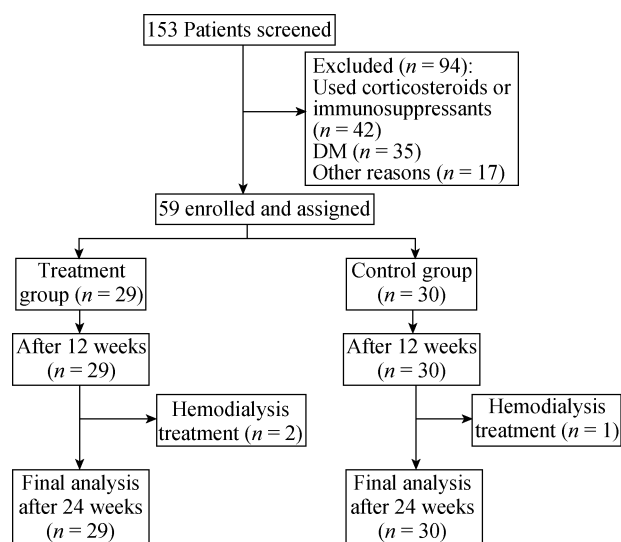


Figure 1. Patient profile. DM: diabetes mellitus.

Table 1. Patient characteristics at baseline.

	Probuocol group (n = 29)	Control group (n = 30)	P
Age, year	44 ± 10	38 ± 13	0.064*
Male: Female	21: 8	16: 14	0.180†
Height, cm	167.72 ± 8.82	169.56 ± 8.84	0.331*
Weight, kg	80.52 ± 14.61	80.68 ± 17.09	0.970*
BMI, kg/m ²	28.30 (25.54–29.40)	27.60 (25.57–30.63)	0.756 [#]
SBP, mmHg	122.0 (116.5–140.0)	130.0 (119.8–140.00)	0.538 [#]
DBP, mmHg	80.0 (78.5–87.0)	80.0 (78.0–88.25)	0.772 [#]
24-h urine protein, g	1.31 (0.41–2.66)	1.42 (0.86–2.55)	0.328 [#]
Albumin, g/L	42.5 (36.9–45.0)	41.6 (37.9–46.3)	0.435 [#]
eGFR, mL/min per 1.73 m ²	68.45 ± 32.03	67.36 ± 43.24	0.913*
Cholesterol, mmol/L	4.58 ± 1.44	4.39 ± 0.67	0.510*
Triglycerides, mmol/L	2.21 (1.47–3.33)	2.09 (1.25–2.72)	0.259 [#]
LDL, mmol/L	2.94 ± 0.69	2.45 ± 1.01	0.035*
C-peptide, ng/mL	3.82 (2.96–4.81)	3.68 (2.95–4.78)	0.915 [#]
Fasting insulin, μU/mL	15.20 (10.02–22.16)	12.89 (10.24–16.73)	0.332 [#]
HOMA-IR	3.70 (2.10–6.00)	3.72 (2.20–4.00)	0.252 [#]
CKD staging			
CKD1	6	9	0.552†
CKD2	13	6	0.054†
CKD3	10	15	0.295†
CKD4	0	0	NA
CKD5	0	0	NA
ARB types			
Losartan potassium	21	23	0.771†
Irbesartan	5	3	0.472†
Olmesartan	3	4	1.000†

Continuous variables were presented as the mean ± SD or median (quartile). Categorical variables were described using frequency and percentage. *Normal distribution, for independent sample *t*-test; [#]Non-normal distribution, for the rank sum test; †Chi-square test. ARB: angiotensin receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HOMA-IR: homeostatic model assessment-insulin resistance; LDL: low density lipoprotein.

Table 2. Indicators between the two group before and after treatment.

	Probuocol group (n = 29)			Control group (n = 30)			P
	Baseline	24 (week)	Differences	Baseline	24 (week)	Differences	
BMI, kg/m ²	28.30	27.30	0.00 (−1.00–0.50)	27.60	27.20	0.00 (−0.54–0.40)	0.690 ^b
Uric acid, μmol/L	422.62	402.76	−19.86 (−52.63–12.9)	423.59	382.49	−41.10 (−70.47 to −11.73)	0.327 ^a
eGFR, mL/min per 1.73 m ²	68.45	79.01	+3.12 (−3.20–10.47)	67.36	63.11	−0.87 (−15.82–6.15)	0.041 ^b
Cholesterol, mmol/L	4.58	3.92	−0.62 (−1.02 to −0.23)	4.39	4.77	+0.34 (−0.02–0.71)	0.001 ^a
Triglycerides, mmol/L	2.21	1.67	−0.11 (−1.18–0.19)	2.09	1.90	−0.14 (−0.85–0.28)	0.481 ^b
HDL, mmol/L	1.05	1.02	−0.03 (−0.17–0.12)	0.85	0.76	−0.02 (−0.18–0.11)	0.952 ^b
LDL, mmol/L	2.94	2.65	−0.20 (−0.55–0.15)	2.45	2.50	+0.06 (−0.23–0.34)	0.245 ^a
C-peptide, ng/mL	3.82	2.98	−0.76 (−1.51–0.22)	3.68	3.63	+0.28 (−0.37–1.19)	0.001 ^b
Fasting insulin, μU/mL	15.20	9.13	−4.63 (−11.17 to −0.64)	12.89	13.42	+1.98 (−0.95–3.92)	< 0.001 ^b
HOMA-IR	3.70	2.00	−1.45 (−2.90 to −0.43)	3.72	3.25	+0.54 (−0.38–1.87)	< 0.001 ^b
24-h urine protein, g/24 h	1.31	0.71	−0.04 (−0.38 to 0.27)	1.42	0.96	−0.34 (−1.17–0.09)	0.070 ^b

Continuous variables were presented as the mean ± SD or median (quartile). Absolute changes were calculated by using the last measurement of value minus the baseline of value. ^aNormal distribution, for independent sample *t*-test; ^bNon-normal distribution, for Mann-Whitney test. BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL: high density lipoprotein; HOMA-IR: homeostatic model assessment-insulin resistance; LDL: low density lipoprotein.

Table 3. Repeated measurement analysis of HOMA-IR index.

	<i>n</i>	0 week	12 week	24 week
Probuocol group	29	1.93–8.65	1.64–5.67	1.21–3.84
Control group	30	1.93–5.17	1.92–6.25	2.16–6.93

Between groups (F, P): 1.360, 0.248; Time (F, P): 5.973, 0.003; Groups × Time (F, P): 22, 0.000. The 1/SQRT (HOMA-IR) formula was used for transformation, the converted data was normal distribution and met homogeneity of variance test. The *P* value of Mauchly’s test of sphericity was 0.265. Inverse operation was done by using the 1/SQ (converted data) formula, the results were presented as the form of interval representation and shown above. HOMA-IR: homeostatic model assessment-insulin resistance.

Table 4. Comparison of change in HOMA-IR index from baseline to 24 weeks between two groups.

	Probuocol group (<i>n</i> = 29)	Control group (<i>n</i> = 30)	<i>P</i>
Baseline	3.70	3.72	0.252
Last measurement	2.00	3.25	0.001
Change in HOMA-IR	-1.45 (-2.90 to -0.43)	+0.54 (-0.38–1.87)	< 0.001
Percentage change (%)	-47	+15	

HOMA-IR: homeostatic model assessment-insulin resistance.

HOMA-IR index. After 24 weeks, the reduction rate of the HOMA-IR index in the probuocol group was 47%, and the increase rate in the control group was 15%. Figure 2 integrates the major data in Table 4 and the description of HOMA-IR, changes in HOMA-IR values, and the C-peptide assays in these two groups using line graphs.

3.5 Observation of the safety of the patients

The mean baseline blood pressure in the probuocol group was 122/80 mmHg, and the mean baseline blood pressure in the control group was 130/80 mmHg. After 24 weeks, the mean blood pressure in the control group was 128.9/81.8 mmHg, and the mean blood pressure in the probuocol group was 127.3/82.5 mmHg; blood pressure did not exhibit significant changes during the study. The CKD staging between these two groups did not exhibit significant changes at baseline. The types of ARB used after 12 and 24 weeks also did not exhibit significant differences. Regarding safety observations, during the study process, four patients (one in the treatment group and three in the control group) had mild to moderate gastrointestinal discomfort; there were no adverse reactions, such as headache, dizziness, and rash. There were also no severe adverse reactions, such as a prolonged QT interval in the electrocardiogram and ventricular tachycardia. No patient stopped medication because of an adverse reaction.

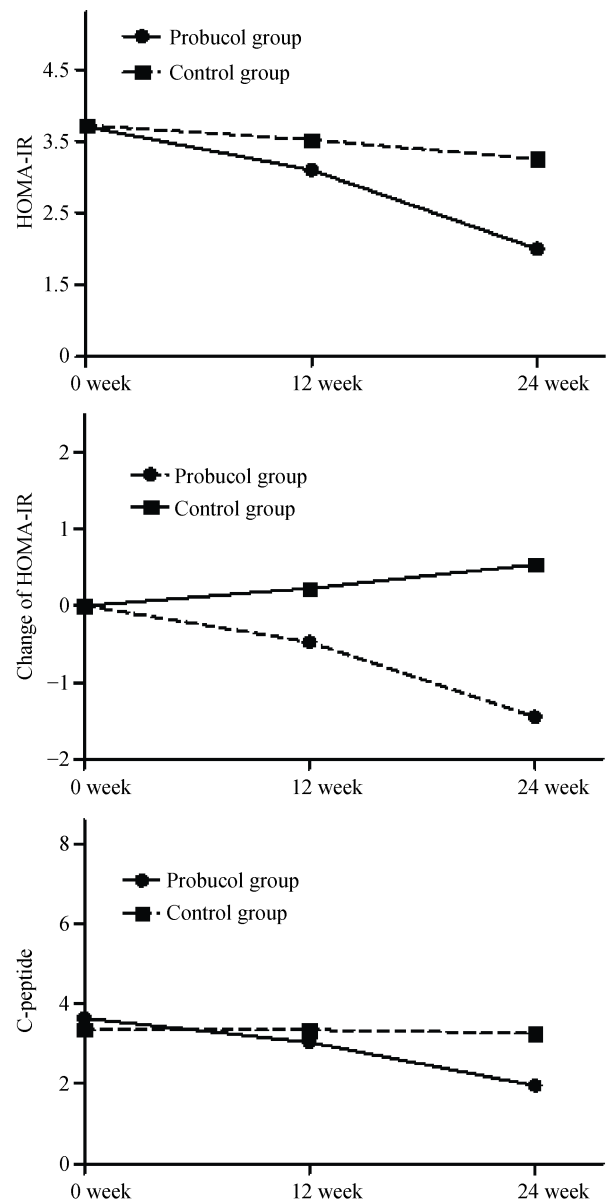


Figure 2. Absolute and relative change in HOMA-IR and C-peptide levels in the two study groups from baseline to 24 weeks. HOMA-IR: homeostatic model assessment-insulin resistance.

4 Discussion

The findings of this study demonstrate that probuocol is well-tolerated and effective in non-diabetic subjects with CKD and IR. Probuocol treatment has been shown to decrease the HOMA-IR index and to decrease the reduction rate of eGFR. Probuocol is a unique cholesterol-lowering drug with antioxidant, anti-inflammatory, and anti-atherogenic properties.^[15] However, the action mechanism of pro-

bucol has not yet been elucidated in detail. To the best of our knowledge, probucol has never been studied specifically in non-DM CKD patients with IR, and data on its effects in CKD patients are very limited.

This study also shows that there are clear differences in the lipid levels of cholesterol between the two groups. Probucol, which acts by increasing the rate of LDL catabolism, reduces LDL-cholesterol and HDL-cholesterol simultaneously and enhances reverse cholesterol transport through the activation of reverse cholesteryl ester transport protein and class B type 1 scavenger receptors (SR-B1).^[16-18] In this study, HDL and LDL decreased in the probucol group, but the difference between the two groups was not significant. This may be because of significant differences and non-experimental factors that were present between the two groups at the beginning of the study.

The main pharmacological effects of probucol are its lipid-lowering and antioxidant abilities. One study on 204 acute coronary syndrome patients investigated the protective effects of probucol on contrast-induced nephropathy. Using randomized, controlled methods, the serum creatinine and cystatin C concentrations in the probucol and control group were measured; the results indicated that probucol effectively reduces the incidence of contrast-induced acute kidney injury in this high-risk population.^[19] The study of Zarnardo, *et al.*^[20] on diabetic rats showed that probucol might repair leukocyte-endothelial cell interaction by regulating the expression of adhesion molecules, such as intercellular adhesion molecule-1 and P-selectin, thus ameliorating diabetic kidney damage. Current studies on probucol mainly target DM patients; however, its significance in non-diabetic CKD patients is worth exploring. Our basic studies showed that probucol might improve IR in non-diabetic rats; this clinical study further used controlled studies to investigate the efficacy and safety of probucol on IR in non-DM CKD patients.

This clinical study enrolled a total of 59 patients who met the criteria of non-DM CKD. They all received more than three months of ARB treatment at a constant dose. The treatment group received 0.5 g probucol twice daily for 24 weeks. The results of this study showed that adding probucol treatment to a baseline of ARB significantly reduced the HOMA-IR index in the treatment group compared to the control group that only received ARB ($P < 0.01$), suggesting that probucol could help reverse IR in non-DM CKD patients. In addition, this study showed that compared to patients who only received ARB, patients who received combined ARB and probucol treatment exhibited significantly improved eGFR and significantly reduced blood lipids, such as cholesterol, further suggesting that probucol not only

affects the development and progression of kidney diseases but also exerts a specific kidney protective effect.

For the selection of the control group, it is currently recognized that the RAS system affects the development and progression of kidney diseases. The ACEi/ARB (Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) drugs are RAS blockers; they can effectively relieve high pressure, high perfusion, and high filtration status of glomeruli and delay CKD progression.^[21] ARBs can also activate PPAR- γ to improve IR.^[22] However, our results showed that ARBs had limited efficacy on IR in non-diabetic CKD patients. After receiving more than three months of ARB treatment at a constant dose, the enrolled patients still exhibited abnormal IR; therefore, they were used as the control group. This study also used a constant dose of ARB and balanced blood pressure to reduce the effects of these factors on efficacy. Studies have shown that the control of body weight may reduce IR; therefore, we excluded the effect of BMI at baseline and educated patients about diet and body weight control to exclude the influence of BMI on the experimental results during the study.

For safety, the most important side effect of probucol is the possibility of causing a prolonged Q-T interval on an electrocardiogram.^[23] This study treated patients with 0.5 g twice a day to ensure the safety of the patients. No treatment was terminated because of safety events throughout the follow-up process.

The inclusion and exclusion criteria in this study were relatively rigid. However, because of the small sample size, the conclusions of the study data might exhibit a certain selection bias. In the future, we hope to include a large sample size and perform a multi-center follow-up study.

In summary, this study showed that for non-diabetic patients, the administration of probucol (1 g/day) added to a baseline of ARB treatment significantly decreased the HOMA-IR index, ameliorated IR, reduced the total cholesterol, decreased the reduction rate of eGFR, exerted a certain kidney protection function, and delayed CKD progression. No unsafe events occurred. These results indicate that probucol might have good prospects in clinical applications; therefore, its kidney protection effects and the underlying mechanisms are worth further investigation.

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