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ORIGINAL RESEARCH

BOLD MRI to Evaluate the Effects of Sacubitril/Valsartan on Renal Protection in Type 2 Diabetics

Limin Zhai[1], Yue Wang[1], Li Xiang[2], Liang-ping Ni[2], Deyuan Zhang[1], Tianrong Pan[1]

[1]Department of Endocrinology, The Second Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China; [2]Department of Radiology, The Second Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China

Correspondence: Tianrong Pan; Deyuan Zhang, The Second Affiliated Hospital of Anhui Medical University, No. 678 Furong Road, Hefei, Anhui Province, 230601, People's Republic of China, Email ptr1968@163.com; 61118979@qq.com

Objective: To investigate the effects of sacubitril/valsartan on diabetic nephropathy patients by blood-oxygenation-level dependent-magnetic resonance imaging (BOLD-MRI).

Methods: Forty-eight Patients with diabetic kidney disease (DKD) admitted to our hospital from April 2023 to December 2024 were selected. They were divided into two groups based on the treatment obtained. The dapagliflozin group included dapagliflozin 10 mg once daily, and the Sacubitril/valsartan group included a combination of dapagliflozin and sacubitril/valsartan for 12 weeks. The plasma and urine biochemistry parameters of all patients were compared. Meanwhile, renal was scanned by BOLD MRI before and after experiment endpoint.

Results: After 12 weeks treatment, biochemical indexes from baseline were improved in both dapagliflozin group and sacubitril/valsartan group. Sacubitril/valsartan treatment significantly reduced UACR and UNAG excretion, as well as decreased the R2* values of the kidney medulla, compared to the dapagliflozin group ($p < 0.05$).

Conclusion: Sacubitril/valsartan can provide protection in DKD by reducing UACR and UNAG excretion while improving the oxygenation of the medulla area of the kidney, beyond its hypoglycemic and antihypertensive effects.

Keywords: BOLD MRI, Sacubitril/valsartan, diabetic kidney disease, natriuretic peptide

Introduction

Diabetic kidney disease (DKD) represents one of the most severe microvascular complications associated with diabetes and stands as the primary cause of end-stage renal disease.[1] The diagnosis and management of DKD constitute a pivotal aspect in diabetes treatment strategies. Renal biopsy, although definitive, is infrequently employed due to its invasive nature, while indices such as the estimated glomerular filtration rate (eGFR) and urinary microalbumin exhibit limitations in clinically diagnosing and assessing DKD.[2] BOLD MRI utilizes the difference in paramagnetic properties between oxygenated hemoglobin and deoxygenated hemoglobin as an intrinsic contrast, with changes in deoxygenated hemoglobin levels in the blood serving as the foundation for imaging, to evaluate oxygen-related changes caused by diseases. Studies have demonstrated the application of BOLD MRI in assessing renal tissues of diabetic model rats. Human studies have further confirmed that compared to healthy individuals, patients with type 2 diabetes exhibit a hypoxic state in their kidneys, characterized by significantly elevated R2* values in both the renal cortex and medulla. By detecting early alterations in blood perfusion and cortical/medullary oxygenation in diabetic nephropathy, this technique provides a non-invasive method for assessing renal function.[3–5] In the realm of pharmacotherapy, extensive research has been dedicated to discovering novel strategies to halt the progression of DKD. In recent times, the effects of the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide (NP) systems has garnered significant attention. Sacubitril/valsartan, a combination therapy encompassing an inhibitor of neprilysin (sacubitril), which degrades natriuretic peptides, and an angiotensin II type 1 receptor blocker (valsartan), has demonstrated efficacy in delaying heart failure progression in patients.[6] Currently, the beneficial effects of sacubitril/valsartan in diabetic patients with heart failure have been documented,[7]

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yet its impact on DKD remains understudied. Our investigation aims to compare the renal functional effects of sacubitril/valsartan versus dapagliflozin in patients with DKD utilizing BOLD MRI, with the objective of identifying a novel therapeutic intervention to slow the progression of DKD.

Methods

Eligibility and Recruitment

Patients with type 2 diabetes with DKD admitted to our hospital from April 2023 to December 2024 were selected.

Inclusion criteria: 1) Patients with T2DM were diagnosed according to the diagnostic criteria of diabetes established by WHO in 1999. 2) UACR≥30mg/gCr was checked twice before admission and after admission, and the interval between the two examinations was 3–6 months; 3) eGFR≥ 45mL/min/1.73m2.

Exclusion criteria included: 1) T1DM, 2) severe liver insufficiency, heart insufficiency, acute cerebrovascular accident, 3) a history of primary and secondary renal disease and urinary obstruction other than diabetes, such as glomerulonephritis, nephrotic syndrome, lupus nephritis, urolithiasis, renal artery stenosis, urinary tract infection or genital fungal infection; 4) recent cases of ketoacidosis, hyperglycemic hyperosmolar coma and lactic acidosis; 5) cancer, blood system and connective tissue diseases. The patients in the study had signed informed consent. The protocol was approved by medical ethics committee of the Second Affiliated Hospital of Anhui Medical University.

Sample Size Calculation

The sample size was calculated based on effects of Sacubitril/valsartan on renal tissue oxygenation in comparison with dapagliflozin by BOLD MRI. Using the sample size calculation formula for comparing means between two independent samples to calculate sample size: $n = 2(SD)^2 \times (Z_{1-\alpha/2}+Z_{1-\beta})^2/(\mu 1-\mu 2)^2$. $\mu 1-\mu 2$: expected mean difference between the two groups (effect size); SD: combined standard deviation; $Z_{1-\alpha/2}$ and $Z_{1-\beta}$: standard normal distribution quantiles ($Z_{0.975}= 1.96$ for $\alpha = 0.05$; When $\beta = 0.2$, $Z_{0.8}= 0.84$). The sample computation was based on data available from the study by Saijun Zhou et al.[8,9] Assuming a 15% improvement, with a two-sided $\alpha = 0.05$ and 80% power, the required sample size was 19 per group. Accounting for a dropout rate 10%, combined with other previous studies.[10,11] The sample size in our study was 50, of which 1 case was lost to follow-up, 1 case was discontinued for economic reasons, and 48 patients were finally included.

Study Protocol

Treatment protocols for hospitalized patients in accordance with the "Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition)". Based on the treatment regimen obtained, patients were categorized into Group 1 if their regimen comprised dapagliflozin (10 mg once daily) but excluded sacubitril/valsartan, while also meeting our inclusion and exclusion criteria. The patients in Group 1 were sequentially numbered, and using the random number table method, 25 patients were randomly selected to form the control group (dapagliflozin group). This selection process involved random sampling. Similarly, patients whose treatment regimen encompassed both dapagliflozin and sacubitril/valsartan (100 mg once daily), and fulfilled our inclusion and exclusion criteria, were assigned to Group 2. These patients were also sequentially numbered upon enrollment. Subsequently, 25 patients were randomly selected from Group 2 using the random number table method to constitute the treatment group (sacubitril/valsartan group). This component of the study also involved randomization. These selected patients were examined by Bold MRI and followed up for 12 weeks. Hypoglycemia events and other adverse reactions were recorded.

Measurement of Plasma and Urine Biochemistry

At beginning of the protocol, gender, age, duration of diabetes, comorbidities and drugs using of patients were calculated. The Clinical datas such as FBG (fasting blood glucose), HbAlc (glycosylated hemoglobin), TG (triglyceride), TC(cholesterol), TyG (Triglyceride glucose index), eGFR, SBP (systolic blood pressure), DBP (diastolic blood pressure), UACR (the ratio of urinary albumin and creatinine) and UNAG (urine N-acetyl-beta-d glucosidase) were calculated at begins and ends of the study. HbA1c was tested by using High performance Liquid Chromatography (HPLC) (Shanghai, ADAMS, CO. Ltd, China). FBG by the hexokinase method, TG by the GPO-POD method, TC by

the enzymatic method (Beckman Coulter, USA). Urinary albumin by immunoscattering turbidimetry method. Urinary creatinine by the creatine oxidase method and UNAG by the P-nitrophenol colorimetry method (Shenzhen, Guosai Biotechnology Co., LTD China).

Renal BOLD MRI

Magnetic Resonance Scanning Method

Siemens MAGENTOM Vida 3.0T superconducting MRI scanner with 32-channel phased array coil was adopted. The respiratory gating was placed in the area with the greatest amplitude of abdominal respiratory movement. Coronal BOLD MRI was performed for patients with no organic lesions found at the end of routine MRI scan. MRI scanning sequence parameters: haste sequence was adopted for coronal T2WI, TR 1000 ms, TE 83 ms, (field of view, FOV) 400mm×400mm, NEX 1, layer thickness 6 mm, layer spacing 1.2 mm, matrix 384×307, layer number 15. In axial position T2WI-FS, haste sequence was adopted, TR 1600 ms, TE 96 ms, FOV 380mm×312mm, NEX 1, layer thickness 6 mm, layer spacing 1.2 mm, matrix 384×250, layer number 25. TSE sequence was adopted for axis T1WI, TR 4 ms, TE 1.29 ms, FOV 380mm×312mm, NEX 1, layer thickness 4 mm, layer spacing 0.8 mm, matrix 320×195, layer number 30. EPI sequence was used for R2* MAP scan (BOLD MRI), TR 284 ms, TE 2.46 ms, FOV 400mm×400mm, NEX 1, layer thickness 6 mm, layer spacing 1.2 mm, matrix 160×160, layer number 15. Before the kidney BOLD MRI scan, fasting was required for more than 10 hours. Subjects began to hold their breath at the end of the exhalation and maintained during the scan. After the scan, the original data is transferred to the Siemens post-processing work station to obtain the R2* graph.

Image Processing Method

Six total regions of interest (ROI) (3 in cortex and 3 in medulla) were defined at the upper, middle and lower poles of both kidneys in the medulla and cortex based on the anatomical images. Each ROI excluded the renal margin, renal column, renal sinus fat, blood vessels, etc. The mean values of renal cortex (CR2*), medulla (MR2*) and R2* ratio between medulla and cortex (MCR) were measured by two experienced attending physicians of the imaging department were statistically analyzed.

Statistical Analysis

SPSS 26.0 statistical software was used for data analysis, and the measurement data were presented as mean ± standard deviation. *T*-test was used for comparison between groups. Non-normal distribution of measuring materials in the median number and interquartile distance [M (QL, QU)] indicates. The rank sum test is used for inter-group comparison. The statistical data were expressed as rate (%) and $\chi 2$ test was used. Alpha = 0. 05 is the test level.

Results

Comparison of Clinical and Biochemical Index Between the Two Groups Before Treatment

In the control group, there were 17 males and 8 females, the average age was (48.83±12.94) years. In the treatment group, there were 17 males and 6 females; the average age was (55.26±10.05) years. There was also no significant difference in terms of duration of diabetes, comorbidities, medications, BMI, HbA1c, FBG, blood lipids, TyG, eGFR, SBP and DBP. Baseline UACR and UNAG were not statistically significant between the two groups (all $P > 0.05$). The baseline clinical characteristics of each group are shown in Tables 1 and 2.

Changes of Biochemical Indexes from Baseline in Two Groups

HbA1c, FBG, blood lipid and blood pressure of the patients decreased after treatment for 12 weeks in both groups, as shown in Table 3. Level of eGFR in both group improved after treatment, while changes of above index levels from baseline were similar in the two groups, all with a $P > 0.05$.

Table 1 Comparison of Baseline Data Between the Two Groups

	Dapagliflozin Group (n=25)	Sacubitril/valsartan Group (n=23)	t/χ2	*P-value*
Gender(M/F)	17/8	17/6	0.408	0.523
Age(Years)	48.83±12.94	55.26±10.05	−1.780	0.082
Duration of diabetes(Y)	9.21±5.43	10.63±5.40	−0.853	0.398
Comorbidities				
Hypertension	12	17	3.840	0.050
Hyperlipemia	15	14	0.524	0.770
Hypoglycemic drugs				
Metformin(%)	12	13	0.751	0.423
Acarbose(%)	3	1	0.606	0.322
Thiazolidinedione(%)	1	1	1.000	0.744
Dipeptidyl peptidase-4 Inhibitor(%)	4	4	1.000	0.623
Glucagon-likePepfidase-1 receptor agonist(%)	12	13	0.751	0.423
Insulin(%)	20	19	1.0000	0.744
Antihypertensive drugs				
Calcium antagonists(%)	10	7	0.042	0.837
Other antihypertensive drugs	2	5	1.733	0.188
Lipid regulating drugs				
Fenofibrate(%)	5	3	0.506	0.477
Statin(%)	10	11	0.223	0.636

Note: P-value: sacubitril/valsartan group versus dapagliflozin group.

Table 2 Comparison of Clinical and Biochemical Index Between the Two Groups Before Treatment

	Dapagliflozin Group (n=25)	Sacubitril/valsartan Group (n=23)	*P-value*
BMI(kg/m2)	27.19±4.75	27.19±4.70	0.998
HbA1c(%)	9.45±1.84	9.09±1.73	0.516
FBG(mmol/L)	8.405(6.748,9.335)	7.525(5.045,10.013)	0.289
TG(mmol/L)	2.275(1.325,4.726)	1.71(1.02,3.10)	0.109
TC(mmol/L)	5.02(4.510,6.900)	4.98(4.20,6.34)	0.463
TyG	9.71±0.92	9.21±0.64	0.054
eGFR(mL/min/1.73m2)	137.03±42.52	111.32.±41.95	0.062
SBP(mmHg)	142.33±17.84	146.79±16.61	0.407
DBP(mmHg)	89.17±13.46	85.63±10.70	0.356
UNAG(U/L)	33.00(21.025,80.950)	58.40(39.40,81.20)	0.060
UACR(mg/g)	623.80(80.42,781.71)	816.54(271.82,975.79)	0.276

Notes: P -value: sacubitril/valsartan group versus dapagliflozin group.
Abbreviations: BMI, Body mass index; HbAlc, glycosylated hemoglobin; FBG, fasting blood glucose; TG, triglyceride; TC, cholesterol; TyG, Triglyceride glucose index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; UNAG, urine N-acetyl-beta-d glucosidase; UACR, the ratio of urinary albumin and creatinine.

Changes of UACR and UNAG excretion levels from baseline were different in the two groups. The reduction of UACR and UNAG excretion levels from baseline in sacubitril/valsartan group significantly were more than that in dapagliflozin group (p = 0.028, 0.000). See Table 3.

Table 3 Changes of Biochemical Indexes From Baseline

	Dapagliflozin Group (n=25)	Sacubitril/valsartan Group (n=23)	P- value
HbA1C	1.60(0.83,3.08)	1.80(0.50,2.30)	0.616
FBG(mmol/L)	1.57(0.25,4.15)	1.18(−0.65,3.50)	0.640
TG(mmol/L)	0.14(−0.03,1.63)	0.57(0.15,1.82)	0.250
TC(mmol/L)	1.03±1.25	1.45±1.01	0.235
eGFR(mL/min/1.73m2)	2.29(−14.18,14.06)	8.02(−40.34,25.98)	0.714
SBP(mmHg)	25.96±16.65	27.58±15.48	0.74
DBP(mmHg)	14.29±11.49	10.05±11.89	0.25
UNAG(U/L)	4.50(2.70,8.60)	11.95(4.55,14.48)*	0.028
UACR(%)	10.01(5.71,14.71)	27.18(18.21,42.75)#	0.000

Notes: P -value: sacubitril/valsartan group versus dapagliflozin group, * P<0. 05, #P<0. 01.

Changes of CR2*and MR2* in the Two Groups Before and After Treatment

Consistency of measurement data: The consistency of CR2* and MR2* measured by two physicians was good (ICC=0.807, 0.843).

Image description The BOLD MRI images of kidney in the subjects of the two groups were clear. Figure 1A–D depict the R2* images and pseudo-color images of the kidney before and after treatment in the dapagliflozin group, respectively. Similarly, Figure 2A–D present the corresponding images for the sacubitril/valsartan group. The white arrow is the renal cortex of low-signal. The white circle is the medulla of the high-signal. Signals of the cortex and medulla of the kidney were reduced in both groups after treatment.

The value of R2* analysis Table 4 indicates that the medulla R2* values were higher than the cortical R2* values in the same group during the same period. The R2* value of left cortex was slightly higher than that of right cortex. Before

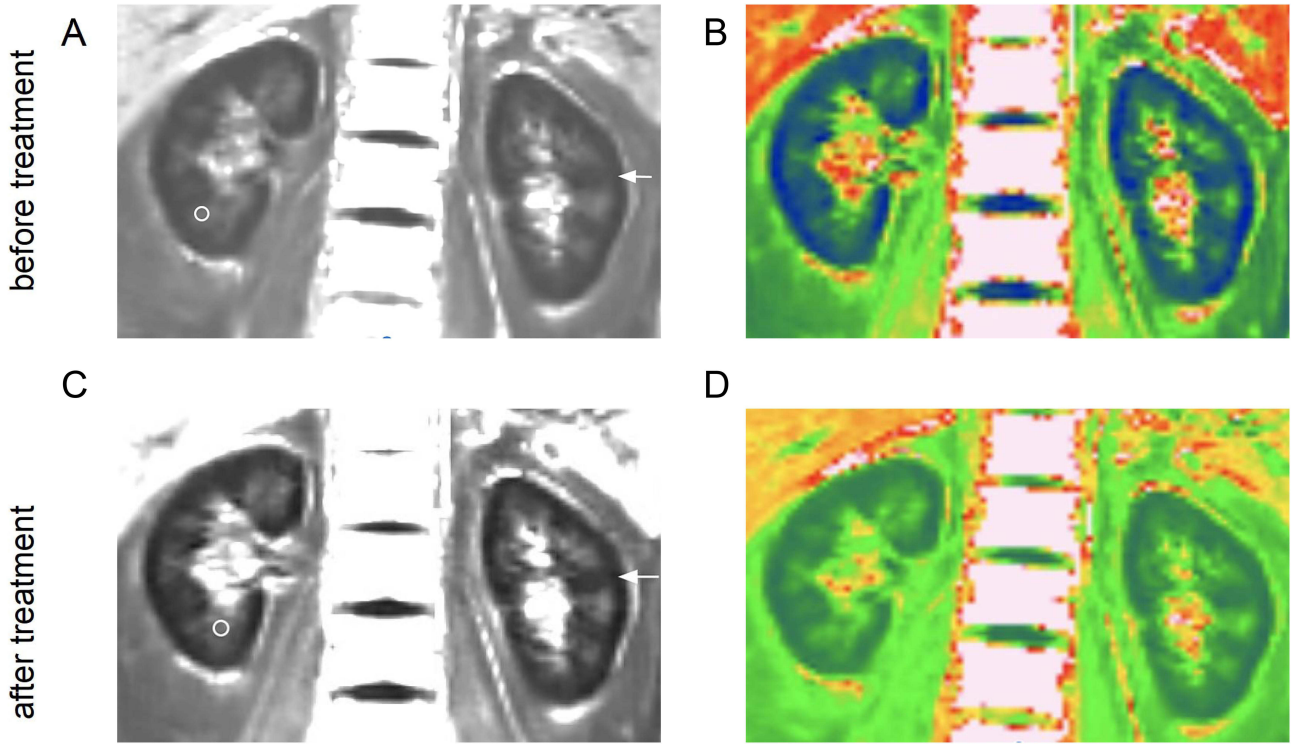

Figure 1 The BOLD MRI images of kidney in dapagliflozin group. (**A** and **B**) the R2* images and pseudo-color images of the kidney before treatment in the dapagliflozin group, (**C** and **D**) the R2* images and pseudo-color images of the kidney after treatment in the dapagliflozin group. Cortex (white arrow) and medulla (white circle).

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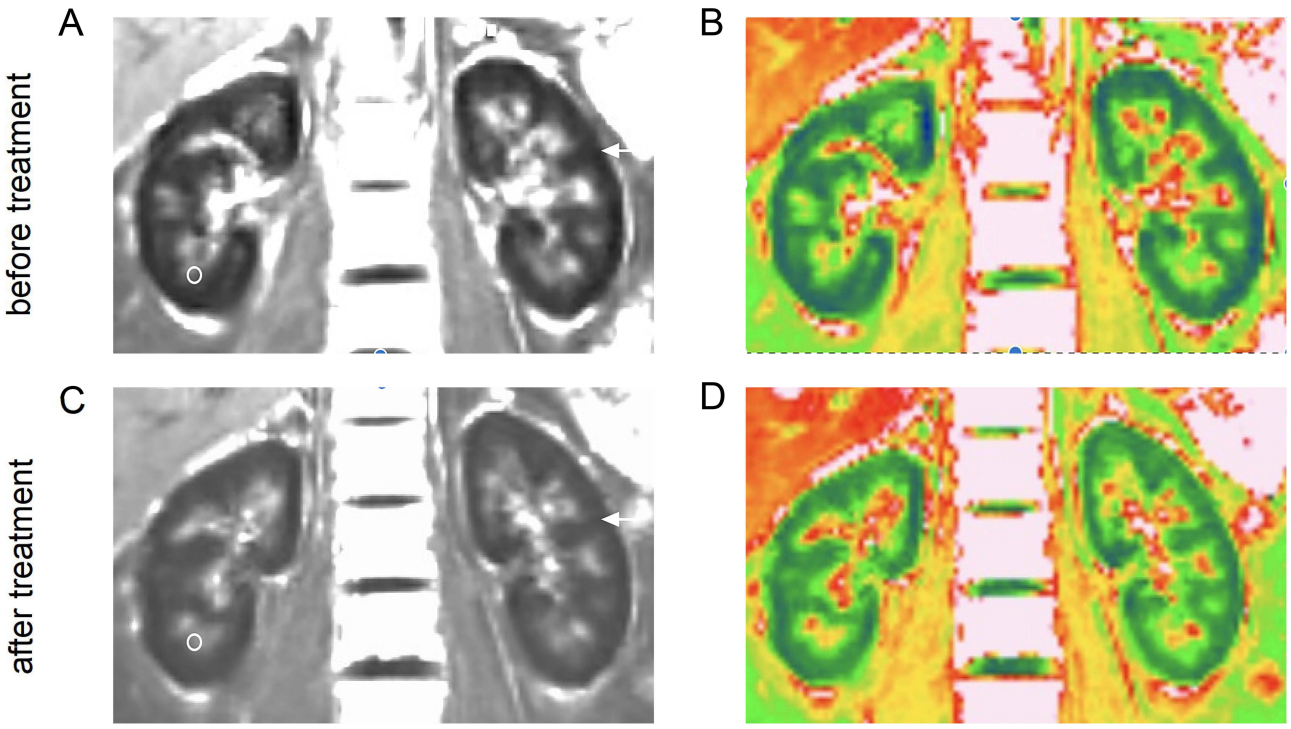

Figure 2 The BOLD MRI images of kidney in sacubitril/valsartan group. (**A** and **B**) the R2* images and pseudo-color images of the kidney before treatment in the sacubitril/valsartan group, (**C** and **D**) the R2* images and pseudo-color images of the kidney after treatment in the sacubitril/valsartan group. Cortex (white arrow) and medulla (white circle).

treatment, the level of CR2*and MR2* in two groups was no statistically significant difference. After treatment, the level of CR2*and MR2* in both group showed a marked decrease. Compared with changes from baseline in dapagliflozin group, Sacubitril/valsartan significantly reduced renal MR2* and MCR values (7.77±3.09 vs 4.62±1.54; 0.21±0.25 vs 0.07±0.15, changes versus dapagliflozin group, p=0.005, p=0.023). (Table 4)

Safety Evaluation of the Two Groups

During follow-up, no DKA and hypoglycemic events (blood sugar < 2.8 mmol/L, serious awareness of needing help from others Obstacles) occurred in both groups. One patient in the treatment group had hypotension, which was relieved after reducing the drug dose. Mild hyperkalemia occurred in 1 case. After drinking more water, retest returned to normal. In the control group, 2 patients had a slight increase in creatinine, which returned to normal after rehydration.

Table 4 Changes of CR2* and MR2* in the Two Groups Before and After Treatment ($\bar{x} \pm s$)

		CR2*		MR2*		Mean		MCR
		R	L	R	L	CR2*	MR2*	
Dapagliflozin group	Baseline	14.29±2.11	14.98±2.16	25.51±3.67	26.49±3.86	14.84±1.87	26.00±3.56	1.75±0.26
	After treatment	12.81±1.43	12.99±2.46	21.36±3.07	21.39±3.33	12.90±1.49	21.38±2.61	1.70±0.24
	Change	1.88±1.05	2.40±2.12	4.15±1.70	5.08±3.21	2.43±1.93	4.62±1.54	0.07±0.15
Sacubitril/valsartan group	Baseline	15.27±2.52	15.87±2.69	28.42±4.2	29.03±4.43	15.75±2.40	28.73±4.11	1.87±0.28
	After treatment	12.05±1.27	13.65±3.18	20.02±3.43	21.89±2.75	12.85±1.91	20.96±2.01	1.66±0.21
	Change	2.43±11.81	3.00±2.32	8.40±5.30	7.15±3.07	3.13±2.15	7.77±3.09[a]	0.21±0.25[a]

Notes: [a]P -value: change from baseline: sacubitril/valsartan group versus dapagliflozin group.
Abbreviations: CR2*, the mean values of renal cortex; MR2*, the mean values of renal medulla; MCR, R2* ratio between medulla and cortex.

Discussion

Diabetes can cause various chronic complications, with diabetic kidney disease (DKD), being a prominent one. It is the leading cause of end-stage renal failure in China[12] and poses a serious threat to patients' health. In addition to the hypoglycemic effect of diabetes drug treatment, the protective effect of the kidney is emphasized. We chose dapagliflozin treatment as the control group because it is a novel hypoglycemic drug that reduces glucose absorption by the kidney and lowers blood sugar levels by inhibiting sodium-glucose cotransporter 2 (SGLT2) in the kidney.[13] Its renal protective effect has been confirmed,[14] aligning with our study results. In our study, in addition to blood sugar, HbA1c, SBP and DBP decreased significantly, UACR and UNAG also decreased significantly compared with before treatment in the dapagliflozin group.

Changes of FBG, HbA1c, blood lipid (TG and TC), blood pressure and eGFR from baseline in the treatment group were similar to those in the control group. UACR decreased by 27.18% from base value in the treatment group, compared to 10.01% in the dapagliflozin group. The difference between the two groups was statistically significant ($P = 0.00$). UACR is an indicator of clinical diagnosis of DKD,[15] but difficult to accurately reflect the degree of DKD damage and the location of lesions by single detection of UACR. Urinary NAG is a substance that reflects renal tubule injury and has certain value and sensitivity for predicting urinary microalbumin.[16] Zhang Deyuan et al[17] proposed that it is a sensitive marker for the early diagnosis of DKD in T2DM patients. During our treatment, the reduction of UNAG in the dapagliflozin group was lower than that in the treatment group (11.95 vs 4.5 mg/g, $p = 0.028$). This point indicated that sacubitril/valsartan could reduce renal tubule injury and urinary protein, exerting a protective role on the kidney.

The focus of this study was to evaluate the role of sacubitril/valsartan in patients with DKD by Bold MRI. In recent years, with the development of magnetic resonance imaging technology, it can not only reflect the volume and morphological changes of the kidney noninvasively but also evaluate the changes related to kidney function and microstructure such as renal perfusion, oxygenation, metabolism and water molecule diffusion.[18] Since changes in oxygen content of kidney cortex and medulla substance can lead to changes in deoxyhemoglobin content, BOLD MRI is also suitable for evaluating oxygenation of kidney cortex and medulla substance.[19,20] The R2* value of the index is inversely proportional to the tissue oxygenated hemoglobin concentration, which means the higher the R2* value, the lower the partial pressure of oxygen and the lower the tissue oxygen content.[21] Through our research, after treatment, the value of CR2* and MR2* were decreased in both two groups. Changes of cortical R2* values from baseline were similar between the two groups. Medulla R2* decreased significantly from base in the treatment group than that in the dapagliflozin group. It indicated that sacubitril/valsartan could improve the oxygenation capacity of renal medulla.

We analyzed possible explanations for the effects of sacubitril/valsartan on DKD. Valsartan has been proven to be the first-line treatment for early and middle stage DN in clinical.[22] As it can obviously improve glomerular hyperfiltration, significantly reduce local renal inflammation, proteinuria and delay the progression of DN by inhibiting RAAS system.[23,24] Natriuretic peptides (NPs) are an important complement that can antagonize the sympathetic nervous system, reduce renal fibrosis, improve renal hemodynamics, produce natriuretic and diuretic effects, antagonize RAAS, and inhibit the proliferation of mesangial cells and stroma.[25,26] Neprilysin can reduce the level of NPs in the body. Sacubitril, an inhibitor of neprilysin, can increase the level of NPs and enhance the glucagon-like peptide-1 (GLP-1) receptor pathway simultaneously. By inhibiting sodium reabsorption, activating tubuloglomerular feedback, and improving glomerular blood flow, it achieves the effects of protecting the kidneys and delaying the progression of DN.[27,28] VonLueder et al[29] also found that compared with valsartan treatment, the level of NPs were further increased and the blocking effect of RAAS was further enhanced during using sacubitril/valsartan treatment. Additionally, studies of sacubitril/valsartan in animals with chronic kidney disease found that this combination preparation can reduce oxidative stress, inflammation, and fibrosis and improve the inflammatory pathological damage of DN by blocking the generation of angiotensin II through valsartan.[30,31] On the other hand, it has antioxidant, anti-inflammatory, and anti-fibrotic properties for renal protection by enhancing the level of NPs.[32] Sacubitril/valsartan can regulate renal tubular metabolism. By reducing sodium reabsorption (through inhibition of the Na^+/H^+ exchanger NHE3), it decreased the workload of renal tubules, thereby reducing oxygen consumption. It

may also modulate cellular metabolism through the AMPK/mTOR pathway,[33] suppressing abnormal activation of hypoxia-inducible factor (HIF-1).[34]

Studies have shown that sacubitril/valsartan can influence glucose, blood pressure, and fat metabolism.[35–37] In this study, treatment in two groups both reduced blood glucose, blood pressure and lipids in DKD patients. Although there was no statistically significant difference in the improvement of these parameters between the two groups, our findings did not conclusively demonstrate an independent advantage of sacubitril/valsartan in reducing glucose, blood pressure and blood lipids within the context of this study. However, it also demonstrates that sacubitril/valsartan can improve medulla oxygenation and reduce urinary microalbumin and NAG excretion, independently of its hypoglycemic and antihypertensive effects, suggesting a mechanism that warrants further investigation. The limitations of this study include the sample size, short study duration, and the lack of pathway or histological immunofluorescence data. Therefore, larger sample sizes and longer-term studies are needed to validate the renal protective effects of sacubitril/valsartan in DKD patients. Future research should also include: comprehensive pathway analysis, histological validation studies, and immunofluorescence profiling of relevant protein markers. These additional analyses will undoubtedly provide deeper mechanistic insights.

Conclusion

From mentioned above all, sacubitril/valsartan can reduce UACR and UNAG excretion as long as improve the oxygenation of the medulla area of the kidney. So as to play some protection in DKD beyond its hypoglycemic and antihypertensive effects. Specific mechanisms of this effect still need further researches.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

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Disclosure

The authors declare no competing interests in this work.

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