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Case Study of Diabetic Nephropathy Management by Combination Therapy including RAS blocker, DPP-4 Inhibitor and Pentoxifylline

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ABSTRACT

Background: *We introduce two cases of progressive diabetic nephropathy that were successfully managed with combination therapy including RAS blocker(Losartan), DPP-4 inhibitor(Linagliptin), pentoxifyllin. In case 1(Diabetes History 12 years, female, age 50 years, eGFR: 62.38mL/min/1.73m^2, proteinuria:3.3g/d), her eGFR and proteinuria deteriorated(eGFR: 50.54mL/min/1.73m^2, proteinuria:4.3 g/d, annual eGFR change: -17.76mL/min/1.73m^2) after 8 months using of amlodipine and atenolol as BP control agents, we replaced them with losartan and pentoxifylline and could observe some improvement in eGFR change (annual eGFR change: -11.46mL/min/1.73m^2) with slight reduction in proteinuria(3.7g/d). Therefore, we added linagliptin which finally led to significant improvement both in eGFR(55.65 mL/min/1.73m^2) and proteinuria(2.5g/d). In case 2(Dibetes History 10 years, male, age 64 years, eGFR: 59.07 mL/min/1.73m^2, proteinuria: 2.9g/d), he had controled his blood pressure with amlopdine and atenolol but his protienuria and eGFR did worsend after 1 year (eGFR:49.92 mL/min/1.73m^2, proteinruia: 3.6g/d), therefore we replaced amlodipine and atenolol with losartan and added linagliptin for renoprotective and glycemic control measure but there was no significant improvement in eGFR(44.58 mL/min/1.73m^2) so we added pentoxifylline which finally led to improvement in eGFR(53.89 mL/min/1.73m^2).*

Keywords: Diabetic nephropathy, Losartan, Pentoxifylline, Linagliptin.

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INTRODUCTION

Diabetic nephropathy is a leading cause of ESRD (End Stage Renal Disease) which is responsible for No.1 diabetic mortality rate. This diabetic microvascular complication which is clinically characterized by edema, hypertension and proteinuria accounts for 15-25% of all diabetic cases. Once this condition is defined as a progressive form in which consistent proteinuria is a main clinical manifestation, this will lead to ESRD over a short period of time [1, 2]. Although some BP control and glycemic control agents such as renin–angiotensin–aldosterone system (RAS) blocker[including angiotensin II receptor blocker(ARB)], glucagon-like peptide-1 (GLP-1) receptor agonist or dipeptidyl peptidase-4 (DPP-4) inhibitor and sodium glucose transporter-2(SGLT-2) inhibitor, pentoxifylline have been reported to have some renoprotective effects on diabetic nephropathy by alone or combined with the others[3-7], combination therapy of ARB, DPP-4 inhibitor and pentoxifylline have not been investigated for renoprotective treatment for Diabetic nephropathy.

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SUBJECT AND METHODS

Case Report 1

On August 15th, 2024, a 50 year old diabetic female patient was admitted to our department with presenting severe edema and hypertension. At admission, her glycemic control was bad with HbA1c level of 11.3%. She had no family history of Diabetes Mellitus. Her physical examination showed significant edema in lower extremities and mild dehydration signs. Her GCS score was 15, blood pressure 160/105mmHg, pulse rate 92min^{-1}, respiration rate 19min^{-1}, body temperature 36.8℃, height 1.6m, body weight 69kg, BMI 26.9kg/m^2. Her eGFR was 62.38 mL/min/1.73m^2, proteinuria was 3.3g/d.

For better glycemic control, we replaced metformin and glibenclamide with insulin and initiated amlodipine and atenolol as BP control measure. Eight months later, her eGFR reduced to 50.54 mL/min/1.73m^2 and protein in urine increased up to 4.3g/d which shows clear deterioration of renal function(annual eGFR change: -17.76mL/min/1.73m^2). She had no history of using any agents which affects renal function such as anagelics and no other renal disorders were confirmed. Therefore, for renoprotective purpose, we replaced amlopine and atenolol with losartan(50mg/d) and added pentoxifylline(800mg/d). 4 months later, her protein in urine reduced to 3.7g/d but her eGFR did not improve (eGFR: 46.72 mL/min/1.73m^2, annual eGFR change: -11.46mL/min/1.73m^2). Therefore, we considered using DPP-4 inhibitor (linagliptin 5mg/d) as adjuvant therapy for both better glycemic control and renoprotetive effect. Thereafter, 16 weeks later, her eGFR had improved up to 55.65 mL/min/1.73m^2 (eGFR change +8.93 mL/min/1.73m^2/year) and protein in urine also improved to be 2.5g/d.

Case Report 2

On May 12th, 2023, a 64 year old diabetic male patient was admitted to our department with presenting severe pain in both legs. His HbA1c level was 9.9%. On physical examination, non-proliferative retinopathy in his left eye and loss of Achilles tendon reflex were detected. His eGFR was 59.07 mL/min/1.73m^2, proteinuria was 2.9g/d. He had had been using metformin and glibenclamide for his glycemic control since his diabetes was diagnosed. For better glycemic control, we replaced metformin and glibenclamide with insulin intensive therapy. One year later, his eGFR reduced to 49.92mL/min/1.73m^2 and protein in urine increased up to 3.6g/d which shows clear deterioration of renal function(annual eGFR change: -9.15 mL/min/1.73m^2). She had no history of using any agents which affects renal function such as anagelics and no other renal disorders were confirmed.

Therefore, for renoprotective purpose, we replaced amlopine and atenolol with losartan(50mg/d) and added linagliptin(5mg/d) for better glycemic control. 12 months later, her protein in urine reduced to 2.8g/d and her eGFR change has improved(eGFR: 44.58mL/min/1.73m^2, annual eGFR change: -5.34 mL/min/1.73m^2). therefore, we added pentoxifylline(800mg/d) for renoprotetive effect. 4 months later, his eGFR had improved up to 53.89 mL/min/1.73m^2 (eGFR change: +9.31 mL/min/1.73m^2) and protein in urine also reduced to 2.1g/d.

RESULTS

Characteristics of Patients

The patients' lab test at admission was shown in the Table 1.

Clinical course of the patients

The clinical course of each patients were shown in the Diagram 1 and 2.

Table 1. Laboratory results at the time of referral.

Examination	Case 1	Case 2
White blood cells (/μL)	8900	6700
Neutrophil (%)	54	61
Lymphocytes (%)	35	32
Monocyte (%)	4	0
Eosinophil (%)	2	5
Basophil (%)	5	2
Red Blood cells (/μL)	310 ×10^4	290×10^4
Platelets (×10^4/μL)	21	19
Hemoglobin (g/dL)	11	10
Hematocrit (%)	34	31
ESR(mm/h)	17	16
ALT	24	31
AST	19	20
HBAsg	-	-
Total protein (g/dL)	6.2	5.4
Albumin (g/dL)	2.4	2.1
TC (mg/dL)	254	219
TG (mg/dL)	168	179
Total bilirubin (mg/dL)	0.23	0.34
Cre (mg/dL)	1.0	1.3
eGFR(mL/min/1.73m^2)	62.38	59.07
CRP(mg/dL)	0.54	0.78
FPG (g/dL)	216	178
HBA1c (%)	11.3	9.9
Urine test		
Protein	3.3	2.9
Glucose	++	+
Red blood cell	4	5
White blood cell	11	9

Diagram 1. Clinical course showing eGFR and proteinuria change of Case 1.

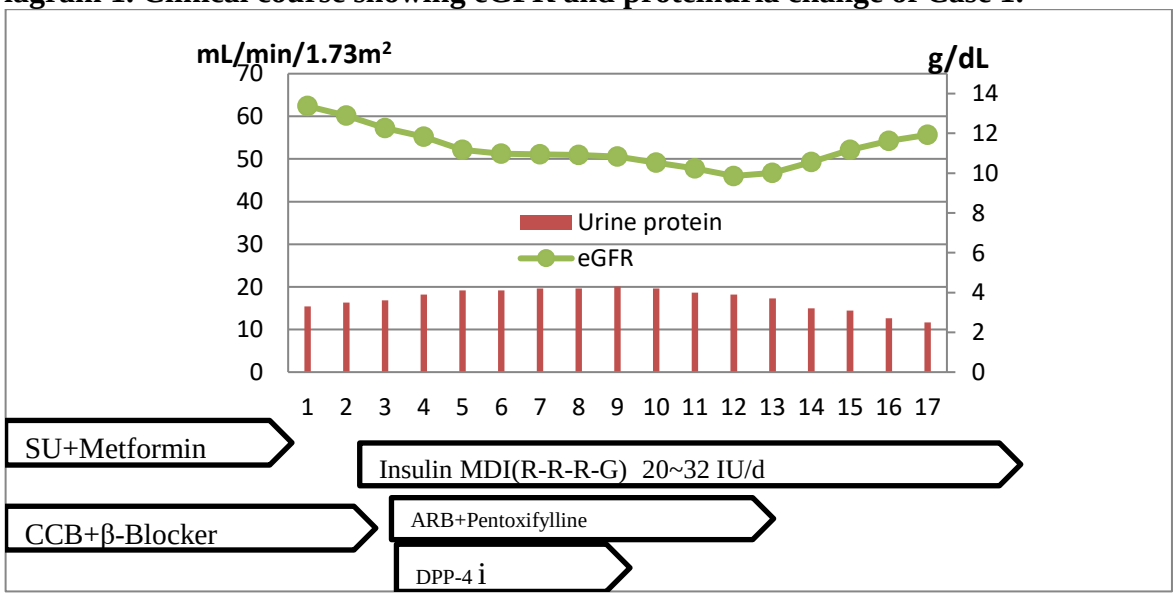
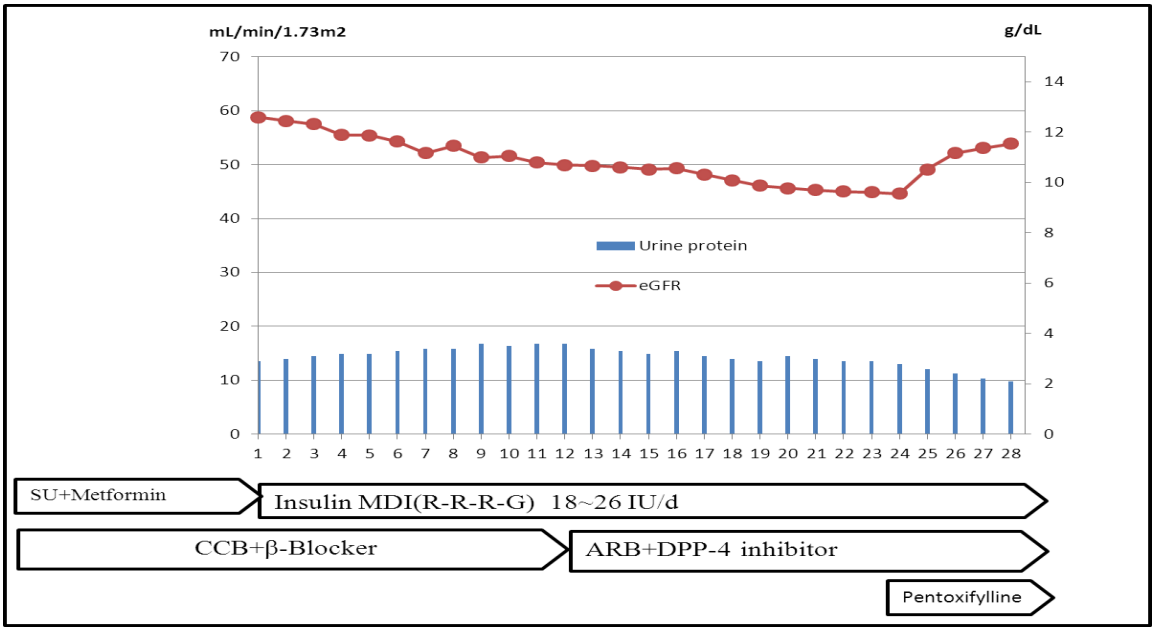


Diagram 2. Clincial course showing eGFR and proteinuria change of Case.



DISCUSSION

We introduced that triple combination therapy including ARB (Losartan), DPP-4 inhibitor(Linagliptin) and pentoxifylline effectively improved renal function of progressive diabetic retinopathy cases.

We confirmed the diagnosis of progressive diabetic nephropathy based on their clinical course, proteinuria level and eGFR decline rate. RAS blockers, DPP-4 inhibitors and pentoxifylline have been reported to have certain renoprotective effects on diabetic nephropathy [3-7] but there have been a little investigations on their combination. ARB has been reported to have renoprotective effect by mechanism of restricting expansion of mesangium and dilation of efferent arterioles of glomerulus[7], DPP-4 inhibitors have been proved to be renoprotective via preventing endothelium cells from damage[3], pentoxifylline's pharmacological mechanism has not been identified clearly but known to improve microcirculation[4-6].

In case 1, we added losartan and pentoxifylline first but eGFR did not improve despite of minor improvement in proteinuria. Therefore, linagliptin was added which led to significant improvements both in eGFR and proteinuria.

In case 2, losartan and linagliptin was added first which also showed positive trend in proteinuria and also lowered annual decline rate of eGFR under 6 mL/min/1.73m^2 but could not prevent reduction of eGFR itself. So we added pentoxifylline which completed the triple therapy of ARB, DPP-4 inhibitor and pentoxifyllin. As a result, eGFR has reversed and protein in urine has reduced significantly.

CONCLUSION

We concluded that if any two of ARB, DPP-4 inhibitors and pentoxifylline were combined for diabetic nephropathy, we couldn't expect sufficient renal function improvement but only when all three of them should be intergrated, we could expect full renoprotective effect which is crucial for early management of dibetic nephropathy.

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