

## New modalities for treatment of diabetic nephropathy: a mini review

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### ABSTRACT

**Background and aims:** Diabetic nephropathy (DN) is the most common cause of end-stage renal failure which could increase the risk of cardiovascular disease and morbidity and mortality in patients. The aim of this study was to investigate new modalities for treatment of diabetic nephropathy.

**Methods:** This study was a mini-review research to investigate drugs that are used for DN treatment.

**Results:** Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptors blocker (ARB) are the bases of DN treatment during recent decades. Due to some of adverse reactions of these drugs like hyperkalemia and chronic cough, other drugs such as non dihydropyridin Ca channel blockers, uric acid lowering drugs, renin antagonists, lipid lowering agents, oral hypoglycemic agents such as Thiazolidinediones, Vitamin D and selective endothelin receptor antagonists have been used in some studies for decreasing proteinuria and slowing progression of DN. The results of these studies are different and controversial in some cases.

**Conclusion:** The cornerstone of diabetic nephropathy is prescription of angiotensin receptor antagonists or angiotensin converting enzyme inhibitors or combination of two classes of drugs. For increasing the antiproteinuric effect of treatment or occurring the adverse effects of these drugs, (especially hyperkalemia), other agents such as Ca channel blockers, direct renin inhibitors, thiolithazons, uric acid lowering drugs or vitamin D may be added or replaced.

**Keywords:** Diabetic nephropathy, Drugs, Treatment.

### INTRODUCTION

Generally, diabetic nephropathy (ICD-10 (2014)= E11.22) could develop in about 30% of type 2 diabetic patients (ICD-10 (2014)= E11) in different communities.<sup>1</sup> After several weeks of initiation of diabetes, glomerular filtration rate increases due to glomerular hyperfiltration (GFR). Later,

after 5-10 years microalbuminuria (urine albumin 30 to 300 mg/day) may develop in some patients. In untreated patients, macroalbuminuria (urine albumin 300 mg/day) usually occurs during 5 to 10 years. At the beginning of macroalbuminuria, GFR may decrease gradually at the rate of 1

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ml/month or 10-12 ml/year, so almost in all of untreated patients, the end-stage renal disease (ESRD) could develop after the additional 5-10 years.<sup>2</sup>

Diabetic nephropathy (DN) is the most common cause of end-stage renal failure in many countries and it is the cause of increasing risk of cardiovascular disease. In patients with DN, urine sediment is usually inactive (bland), but microscopic hematuria can occur in some patients especially in cases of other glomerulopathies.<sup>3</sup> Moreover, severity of proteinuria is variable. So, some patients may suffer from severe nephrotic syndrome up to 20 gr/day.<sup>4</sup> In addition, treatment in micro- albuminuric phase may prevent development of nephropathy; however, in macro albuminuric phase, proper management may just make the progression of ESRD slow or decrease the cardiovascular mortality.<sup>5</sup>

Management of DN may include lifestyle modifications (regular exercise, weight loss in obese patients, restriction of dietary protein intake, limitation of salt and alcohol intake), smoking cessation, blood pressure controlling and adequate blood glucose controlling (glycosylated hemoglobin < 7 percent). Moreover, blood pressure controlling is the other important modality of DN management. Inhibition of the renin-angiotensin aldosterone system with ACE inhibitors or angiotensin II-receptor blockers can also decrease both the blood pressure and proteinuria. Goal of blood pressure management in DN patients is a systolic pressure below 130 mm Hg and a diastolic pressure less than 80 mm Hg, and in patients with proteinuria, it must be greater than 1000 mg/day BP < 125/75. Some studies demonstrated that angiotensin II-receptor blockers may be more effective than ACE inhibitors for decreasing proteinuria and renoprotective effect in micro or macro-albuminuric phases.<sup>6</sup> Combination of angiotensin converting

inhibitors plus angiotensin receptor blockers (dual system blocking) was shown more effective than single agent therapy in some studies.<sup>7,8</sup> However, a large double-blinded clinical trial was carried out on 1448 type-2 diabetic patients and losartan plus lisinopril were prescribed to maximal reduction of proteinuria. Unfortunately, this study was stopped due to significant adverse effects of drugs especially serious hyperkalemia and acute renal failure.<sup>9</sup>

There are new treatment methods for DN patients. For example, Aliskiren, a direct renin inhibitor has the anti-proteinuric effect in diabetic patients.<sup>10</sup> So, Persson and colleagues in a double-blinded clinical trial found that combination of aliskiren and irbesartan had more antiproteinuric effect than monotherapy with another medication in type 2 diabetic patients.<sup>11</sup> The second antihypertensive agents "nondihydropyridin calcium channel blockers" also have the renoprotective effect probably due to decreasing hyperfiltration and intraglomerular pressure.<sup>12</sup>

Third antiproteinuric agent is fibrate, as in small clinical trial, fenofibrate was shown to be effective in reducing proteinuria in addition of lipid lowering property.<sup>13</sup> Vitamin D is the fourth agent, since vitamin D (VD) deficiency probably is a risk factor of deterioration of diabetic nephropathy, so in patients with VD deficiency, replacement of oral VD was shown to be effective in reduction of proteinuria.<sup>14,15</sup> Fifth agent is Allopurinol, as hyperuricemia is also another potential risk factor of cardiovascular and renal mortality; and in comparison with the patients without proteinuria, it has been seen that serum level of uric acid may be greater in DN patients with nephropathy. For example, in the study of Momeni and colleagues, prescription of allopurinol 100 mg/day was shown to be effective in reducing proteinuria in type 2 diabetic patients.<sup>16</sup> As, the sixth medication, spironolactone was used in some studies for

reduction of proteinuria in DN patients.<sup>17,18</sup> Since aldosterone can exacerbate tissue fibrosis especially in patients with heart failure; so it can induce general renal vascular inflammation and glomerulosclerosis probably through profibrotic and proinflammatory cytokines. Spironolactone has not a significant role in declining the blood pressure; in addition, it cannot reduce serum glucose. However; it has probably renoprotective effect due to its anti-inflammatory property. In another study on type 2 diabetic patients, it was found that spironolactone could reduce proteinuria but hyperkalemia may occur. However, combination of hydrochlorothiazide and spironolactone has similar antiproteinuric effect without the adverse effects of hyperkalemia.<sup>17</sup> The seventh new treatment method could be prescription of Thiazolidinediones such as Pioglitazone that may have antiproteinuric effect due to an anti-inflammatory mechanism. Moreover, it may improve the insulin resistance, glycaemic control and lipid profile. However, the studies about the effect of thiazolidinediones mainly were done in rats.<sup>19</sup> The last new treatment modality may be selective endothelin receptor antagonists, due to the adverse effects of Endothelin-1 on kidneys including vasoconstriction, glomerulosclerosis, and induction of cytokine expression.<sup>20</sup> In a study on 211 patients diabetic by de Zeeuw, atrasentan (a selective endothelin receptor antagonist), was tend to the reduction of albuminuria and improvement of blood pressure and lipid profile with manageable fluid overload-related adverse effect in patients receiving RAS inhibitors.<sup>21</sup>

## CONCLUSION

Currently, the cornerstone of diabetic nephropathy is prescription of angiotensin receptor antagonists or angiotensin converting enzyme inhibitors or combination of two classes of drugs. For increasing the antiproteinuric effect of

treatment or occurring the adverse effects of these drugs, (especially hyperkalemia), other agents such as Ca channel blockers, direct renin inhibitors, thioglithazons, uric acid lowering drugs or vitamin D may be added or replaced. It seems that additional double blind clinical trials with long follow-up are needed for declaration of the exact role and determination of long-time effects of these new methods of treatment.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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