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# Diabetic Nephropathy: What is Best Therapeutic Option?

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**Keywords:** Blood pressure; Diabetes; Kidneys; Sodium; Microalbuminuria; Macroalbuminuria; Oxidative stress; Management; Treatment; Reactive oxygen speceis

**Abbreviations:** CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; SNS: Sympathetic Nervous System; RAAS: Renin-Angiotensin-Aldosterone System; ROS: Reactive Oxygen Species; GFR: Glomerular Filtration Rate; ESRD: End Stage Renal Disease; ACEi: Angiotensin Converting Enzyme; ARBs: Angiotensin Receptors Blockers; AT1R: Angiotensin II type 1 receptor'; AT2R: Angiotensin type 2 receptor; DRIs: Direct Renin Inhibitors

## Introduction

The present review focused on the most important metabolic disorder which is affecting every fourth of the diabetic, and is known as diabetic nephropathy. This review focused on the hypertension in diabetic nephropathy, its clinical aspects, management and guidelines. Hypertension is the most common phenomenon in diabetics. It increases the risk of kidney diseases and diabetes and increases the chances for morbidity and mortality. Diabetic nephropathy is the most common cause of Chronic Kidney Disease (CKD) in those with diabetes and is the leading cause for incident end stage renal disease (ESRD). The mechanism of hypertension in diabetic nephropathy is complex, not completely understood, and includes excess accumulation of sodium, sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation and increased oxidative stress. Both non-pharmacological and pharmacological interventions, including RAAS antagonists are critically important in the management of hypertension in diabetic nephropathy.

The purpose of this article is to examine the pathophysiology which leads to hypertension in diabetic nephropathy and the clinical trials that support the implementation of strategies aimed at these pathophysiological mechanisms.

## Diabetic Nephropathy and Hypertension

The hypertension is the condition which is found to be twice in diabetics as compared to the general population [1]. The hypertensive patient's prevalence is also twice as compared to normal patients with respect to diabetes [2]. However, the prevalence of hypertension varies in type 1 and type 2 diabetic subjects according to the micro albuminuria and macro albuminuria levels due to infiltration in kidneys [1]. In type 1 diabetic subjects the hypertension is prevalent in the patients of micro albuminuria and overt nephropathy [2]. While, in case of normoalbuminuric patients the prevalence was found to be somewhat different i.e., 19% [3]. According to one Danish report including 1700 diabetics and 10,000 controls, the prevalence of hypertension (160/95mmHg) was found to be similar to that of the control subjects [2]. The proteinuria and microalbuminuria is considered to be a potential biomarker for diabetic and non-diabetic renal disease [4,5]. In addition to this, the hemodynamic metabolic and genetic parameters which are common in the diabetic patients. Some genes are found to enhance the progression of disease while others are found to be renoprotective [6,7].

## Factors Enhancing Hypertension and Diabetic Nephropathy

Multiple factors contributes to the development of hypertension in type 1 and type 2 diabetic subjects, which results in the dysregulation of the systems that regulate the vascular balances in the body. Various factors like activation of RAAS (Renin Angiotensin Aldosterone pathway), increased Reactive Oxygen Species (ROS), increase in the activity of endothelial

dysfunction and decreased activity of nitric oxide are involved in these derangements. These factors actually increase the activity of non hemodynamic factors that increases the risk of cardiovascular and kidney diseases. The details of these factors are given below:

### Renin angiotensin aldosterone system (raas) pathway

RAAS pathway has been extensively studied with reference to the cardiovascular diseases and hypertension. As there are various enzymes and genes which contribute to the occurrence of not only diabetic nephropathy but also cardiovascular diseases in most of the patients of type 1 and type 2 diabetes. The action of Angiotensin II is mainly responsible for the increase in the vasoconstriction and sodium reabsorption which ultimately increases the blood pressure [8]. The pharmacological drugs are available in the market which inhibits the production of angiotensin II and block AT1R and thus it targets the RAAS pathway.

### Sodium balance

The increase in the sodium plays a very important in hypertension in diabetics and renal disease patients. It has been documented that the people with the renal disease have an increase level of sodium even in the absence of the activity of RAAS pathway [2]. As Glomerular Filtration Rate (GFR) declines, the kidneys ability to filter some important metabolites decreases which continuously increased the level of the sodium thus damage to the glomerular cells [9]. Thus in diabetic nephropathy patients the care must be given with reference to sodium intake and low doses of sodium in diet must be preferred.

### Sympathetic nervous system (SNS) activity

Increased SNS activity results in the increased pathogenesis of diabetic and nephropathy complications. It increases the microalbuminuria and other complications related to diabetes. An increased adregenic activity with high nocturnal blood pressure was also observed in the diabetic nephropathy patients [10-12].

### Nitric oxide

Although the exact role of the nitric oxides are not well documented for hypertensive and diabetic patients. According to some reports the nitric oxide levels are increased in the hyper filtration kidney stages of diabetes. The diabetic rats induced by streptozotocin showed an increased blood pressure by the inhibition of nitric oxide, thus proved that nitric oxide is also one of the factor for hypertension in diabetics [13].

### Oxidative stress

Hyperglycemia is considered to be one of the factors for increased oxidative stress in type 2 diabetic patients [14]. In chronic kidney diseases also there is an increased oxidative stress and decrease antioxidant defenses [3,4]. Reduction in oxidative stress correlates with the albuminuria in the diabetic patients [5]. Through various experimental evidences it was also proved that the reduction in oxidative stress results when the angiotensin II levels becomes low [6]. Nitric oxide in combination with Reactive Oxygen Species (ROS) produces peroxynitrite which is responsible for increase in oxidative stress [7].

### Autoregulatory impairment

In healthy and normal kidneys the auto regulatory functions of the afferent arterioles and juxtaglomerular apparatus are responsible for maintaining the blood pressure. When these mechanisms are impaired as in diabetic nephropathy elevated blood pressure is transmitted to the renal vasculature and it results in the increase in the blood pressure, inflammation, fibrosis, injury and other kidney related impairments. These mechanisms also induced the transport of glucose transporter 1 that is responsible for hyperglycemia in diabetic patients [8].

## Management of Hypertension in Diabetic Nephropathy

### Guidelines

The essential target for the treatment of the diabetic nephropathy is the reduction in the hypertension and albuminuria, as these two parameters are found to be raised in diabetic patients. In type 1 diabetic patients however it was found that 80% of the type 1 diabetic subjects developed due to microalbuminuria and later to macroalbuminuria. Out of these 80% patients about 50-75% of them will develop to End Stage Renal Disease (ESRD) in their next twenty years of life [9]. However for untreated type 2 diabetes mellitus subjects the conditions are somewhat different and about 40% of the patients develop to the overt nephropathy condition whereas the 20% of the type 2 diabetic subjects developed ESRD [10]. Hypertension is considered as the main factor which is responsible for the occurrence of the nephropathy and cardiovascular diseases in both of the type 1 and type 2 diabetic subjects. One drug as the captopril is found to decrease the craetinine levels in diabetic patients with the average decline in creatinine clearance of about 11mL/min/y [11]. For type 2 diabetic patients however the irbesartan resulted in creatinine clearance of 5.5mL/min/yr as compared to 6.8mL/min/yr in the placebo group or in the persons having the treatment of amlodipine [12]. Some Angiotensin Converting Enzyme (ACEi) inhibitors and Angiotensin Receptors Blockers (ARBs) are also found to be more effective in the treatment of diabetic nephropathy which is discussed below.

### ACE inhibitors and ARB blocker as monotherapy

The ACE inhibitors and Angiotensin receptor blockers are considered as the first line of treatment against diabetic nephropathy. The ACE inhibitors are considered as the best treatment for the decrease of the GFR and prevention of albuminuria in type 1 diabetic patient [11,12]. Various types of ACE inhibitor drugs are available for example, enalapril,


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ramipril, captopril, benzapril etc which in combination with renin inhibitors as aliskiren and angiotensin receptor blockers as telmisartin and volsartin are used for controlling diabetic nephropathy [13-15].

### Angiotensin receptor blockers (ARB)

Angiotensin Receptor Blockers (ARBs) are also effective in controlling the hypertension. The mechanism of their action is that they block the Angiotensin II type 1 receptor (AT1R). The AT1R blockade results Angiotensin II to bind to Angiotensin type 2 receptor (AT2R) and it results in the decrease of the blood pressure and also reduced renal interstitial fibrosis [15]. Combination therapy of ARB and ACE inhibitors has been proved in some of the studies to be more beneficial and useful in terms of reducing the hypertension, proteinuria, blood pressure and cardiovascular complications [16].

### Direct renin inhibitors (DRIs)

One of the drugs which is used commonly for the reduction in albuminuria and hypertension in the diabetic nephropathy patients is the Direct Renin Inhibitors (DRIs) pharmacologically named as Aliskiren [17]. For this drug the combination therapy proved to be effective. The losartan and Aliskiren in combination found to be much effective for the reduction of the albuminuria and albuminuria along with albumin to creatinine ratio in type 2 diabetic patients [18]. So, a number of therapeutic trials confers that when the pharmacologically blocking agents block the RAAS pathway, it reduces the risk of progression of diabetes by 20% to 25% and improving cardiovascular conditions [19-25].

## Target Blood Pressure in Diabetic Nephropathy

There were certain retrospective and follow up studies which were conducted to study the effect of blood pressure on renal and cardiovascular diseases. One large study 'The Action in Diabetes and Vascular Disease (ADVANCE) study included 11,140 patients with diabetes and cardiovascular diseases. They were given the ACE inhibitors and thiazide drugs. The incidence of microalbuminuria and creatinine levels were found to be decreased in the patients along with the improvement in systolic blood pressure [26]. This large study thus provide the evidence that the RAAS inhibitors are favourable for the decrease in systolic blood pressure in ESRD and DN patients.

## General Guidelines

Improved blood pressure control and reduction in albuminuria is considered as the main targets when treating the patients of diabetic nephropathy. The Renin Angioten Aldosterne System is one of the major pathway which is involved in the control of the blood pressure. There are certain drugs known as the loop diuretics which are considered as encouraging in reducing the GFR<50mL/min and hyperkalemia. Certain experiments of low sodium diet as well as RAAS inhibitors are also considered as an effective strategy in controlling the progression of chronic kidney diseases in diabetics. The emphasis on the control of salt intake is given because the salt retention is considered as the main reason for enhancement of the glomerulosclerosis and chronic kidney diseases in diabetics. The beta blockers and calcium channel blockers should be recommended for the patients of hypertension. Some drugs like clonidine, vasodilators (hydralazine and minoxodil) and alpha blockers are found to be more effective in patients having the persistent hypertension. The hyperkalemia is found to be effective in patients who are having the thiazide drug treatment [27]. The control of BP below 130/85mmHg in addition to the low sodium intake, with daily dosage of <200mg daily while the persons are on RAAS inhibition is found to be more effective.

## Conclusion

The Diabetic nephropathy is the most common cause of the kidney diseases in the patients with diabetes. Hypertension is highly prevalent in the patients of type 1 and type 2 diabetes. The mechanism which is involved in hypertension in diabetic nephropathy subjects are the activation of the local and renal RAAS, systemic nervous system activity, increased oxidative stress and abnormal no production etc. These mechanisms are responsible for the onset and even worsening of the condition of diabetic nephropathy and they also contributes to the increased risk of cardiovascular diseases. The management for the hypertension and diabetic nephropathy includes the therapies that block the angiotensin production. The blood pressure and treatment goals includes the reduction in blood pressure to 130/80mmHg. For achieving this control the non pharmacological drugs as well as antihypertensive treatment is considered to be more beneficial. However, the overall results of the combination therapies of various drugs of RAAS pathway are still under experimentation.

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