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Review Article

Angiotensin Converting Enzyme (Ace) Inhibitors in the Treatment of Diabetic Nephropathy

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Abstract

Diabetic nephropathy is the renal complication of diabetes which leads to mostly high mortality, especially in diabetic patients. According to World Health Organization, around 90% of people are suffering from type-2 diabetes. It is a progressive and life-threatening condition that has a serious impact on health and life expectancy. There is a worldwide pandemic of type-2 diabetes mellitus and approximately one-third of these individuals develop diabetic nephropathy and shows an enormous economic and social burden to all the countries. Angiotensin converting enzyme (ACE) inhibitors have achieved widespread usage in the treatment of renal disease. They are useful in delaying the progression of diabetic nephropathy. This review discuss the use of (ACE Inhibitors) to prevent or retard the development of diabetic nephropathy. Type-2 diabetic nephropathy is one of the major long-term microvascular complications which occur in nearly 40% of the diabetic patients.

1. INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both and leads to long term multi-organ complications[1]. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. The severe type of hyperglycemia in diabetes leads to abnormality in function, long-term damage, and various major organ failure, like heart, eyes, nerves, kidneys, and blood vessels. There are several pathogenic mechanisms which are involved in the development of diabetes mellitus. India has the world's largest number of diabetic patients and hence termed as the "diabetes capital of the world"[2].

2. TYPES OF DIABETES MELLITUS

There are three types of diabetes mellitus[3]:

- Type 1 diabetes mellitus (IDDM)
- Type 2 diabetes mellitus (NIDDM)
- Gestational diabetes mellitus (GDM)

3. SYMPTOMS OF DIABETES MELLITUS

Symptoms of diabetes are depicted in Fig.1.

4. COMPLICATIONS OF DIABETES MELLITUS

Complications of diabetes include acute and chronic complications. The acute complications are diabetic ketoacidosis, hyperosmolar hyperglycemic non ketotic coma, lactic acidosis and hypoglycemia. The chronic complications include diabetic nephropathy, cardiovascular disease, peripheral vascular disease, cerebrovascular disease, diabetic retinopathy[5].

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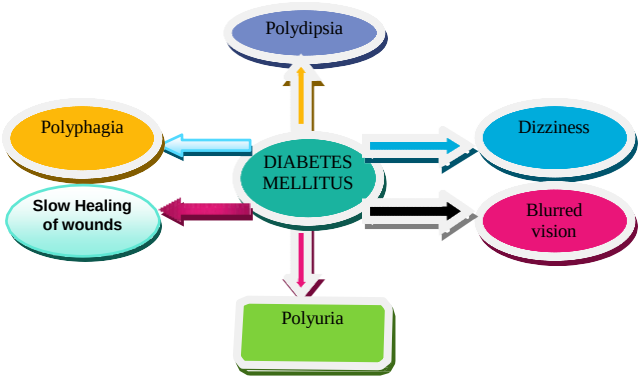

Fig. 1: Symptoms of diabetes mellitus[4]

5. DIABETIC NEPHROPATHY (DN)

Diabetic nephropathy is one of the major or chronic complications and leading cause of end-stage renal disease and its morbidity and mortality is continuously increasing. From a clinical perspective, it is a syndrome characterized by the onset of proteinuria, a subsequent decline in Glomerular Filteration Rate (GFR), and ultimate progression to the renal failure, excessive deposition of extracellular matrix proteins[6] thickening of the peripheral glomerular basement membrane glomerular hypertrophy, tubule interstitial fibrosis, decreased excretion of albumin and decreased creatinine clearance[7]. It is one of the most life threatening diseases worldwide. In clinical, diabetic nephropathy is categorized into different stages which are based on the values of urinary albumin excretion (UAE), macroalbuminuria (MaA) and microalbuminuria MiA[8]. Hyperglycemia and hyper-tension are considered to be the major risk factors which are implicated in the progression of diabetic nephropathy[9]. It is a significant health and economic burden all over the world[10].

6. RENAL STRUCTURAL ABNORMALITIES FOUND IN DIABETIC NEPHROPATHY

There are various kinds of structural abnormalities which are found in renal in diabetic nephropathy[11]:

- Mesangial expansion
- Glomerular sclerosis (diffuse, nodular)
- Fibrin cap lesion
- Capsular drop lesion
- Basement membrane thickening (glomerular and tubular)
- Endothelial foam cells podocyte abnormalities
- Armanni-Ebstein cells (proximal tubules stuffed with glycogen)
- Tubular atrophy
- Interstitial inflammation
- Arteriosclerosis and Interstitial fibrosis.

7. PATHOGENESIS OF DIABETIC NEPHROPATHY

Approximately one third of the diabetic patients develop in to diabetic nephropathy, which is the main reason for chronic kidney disease[12]. The pathogenesis of diabetic nephropathy is complex, and essentially driven by exposure of the kidneys to an altered internal environment, that triggers multiple pathways[13]. Hyperglycemia is the initiating event which causes structural and functional changes such as glomerular hyper filtration, glomerular and tubular epithelial hypertrophy, and micro-albuminuria, followed by the development of thickening in glomerular basement membrane, accumulation in mesangial matrix and over activation of proteinuria, and finally glomerulosclerosis and ESRD (End stage renal disease)[14]. It is mostly associated with hypertension, volume expansion and also due to increased tubular sodium reabsorption. Due to activation of tubular loading in protein, uptake in proximal tubular cells that triggers a pro-inflammatory tubulo-interstitial response leading to progressive tubulo-interstitial inflammation and fibrosis, which is also accelerated by hyperglycemia itself[15].

Various pathways which are involved in diabetic nephropathy are the renin angiotensin aldosterone system (RAAS), formation of the advanced glycation end products (AGEs), polyol pathway and protein kinase C pathway[16].

8. ROLE OF THE RENIN–ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS) IN DIABETIC NEPHROPATHY:

The renin angiotensin aldosterone system (RAAS) is very much involved in most of the pathological processes that leads to development of diabetic nephropathy. In this system there are various subsystems which contribute to the disease pathology. One of these involves angiotensin-I (Ang-I) which are activated during diabetic nephropathy which results in hypertrophy of various renal cells and has a pressor effect on arteriolar smooth muscle resulting in increased vascular pressure. Ang-I also induces apoptosis, cell growth, inflammation, migration and differentiation[17].

Within the afferent arteriole of the kidney, renin is synthesized and released by the juxtaglomerular cells which are responsible for reducing the sodium concentration and intravascular volume[18]. Hydrolysis of angiotensinogen to angiotensin-I (Ang-I) is done by the catalysis of rennin, which is then converted to Ang-II by the angiotensin-converting enzyme (ACE), that is present in the lungs and vascular tissue. Ang-II causes vasoconstriction by acting on vascular smooth muscle, and on the adrenal zona glomerulosa[19] stimulate the aldosterone production . Chronic Ang-II activation may results in development of hypertrophy and hyperplasia and subsequent aldosterone secretion in zona glomerulosa. Angiotensin- II also activates the progression of reactive oxygen species, free radical generation, that leads to renal/vascular endothelial dysfunction, also it induce the expression of chemotaxins, chemokines and cell adhesion molecules, all of which contribute to cell proliferation and renal fibrosis[20].

ACE inhibitors leads to reduce the production of Ang II, a potent vasoconstrictor, leads to lowering the intraglomerular pressure and reduced glomerular hypertension. They are also useful in decreasing the glomerular permeability to urinary albumin which results in decreasing the proteinuria level[21]. The renin-angiotensin aldosterone system (RAAS) and its effector molecule angiotensin II (AII), have a range of hemodynamic and non hemodynamic effects that contribute not only to the development of hypertension, but also to renal disease[22].

Proteinuria reduction is always associated with renal and cardiovascular protection. There is large evidence from animal and human studies which shows that inhibition of the renin–angiotensin system reduces proteinuria[23]. The RAAS has an important biological homeostatic function in maintaining blood volume and salt-water balance, thus affecting the levels of blood pressure and tissue perfusion by a number of various complex actions, which have a global effect of vasoconstriction and sodium retention. This increased pressure results mainly from a differential angiotensin II effect on efferent and afferent glomerular arterioles[24] . The RAAS system must be blocked by a number of therapeutic drugs, like ACE inhibitors, direct renin inhibitors, ARBs, aldosterone antagonists (spironolactone and eplerenone), and prorenin receptor antagonist. These agents reduce glomerulosclerosis, tubulointerstitial fibrosis, albuminuria, and loss of glomerular filtration rate (GFR) in animal experimental models and human randomized clinical trials[25].

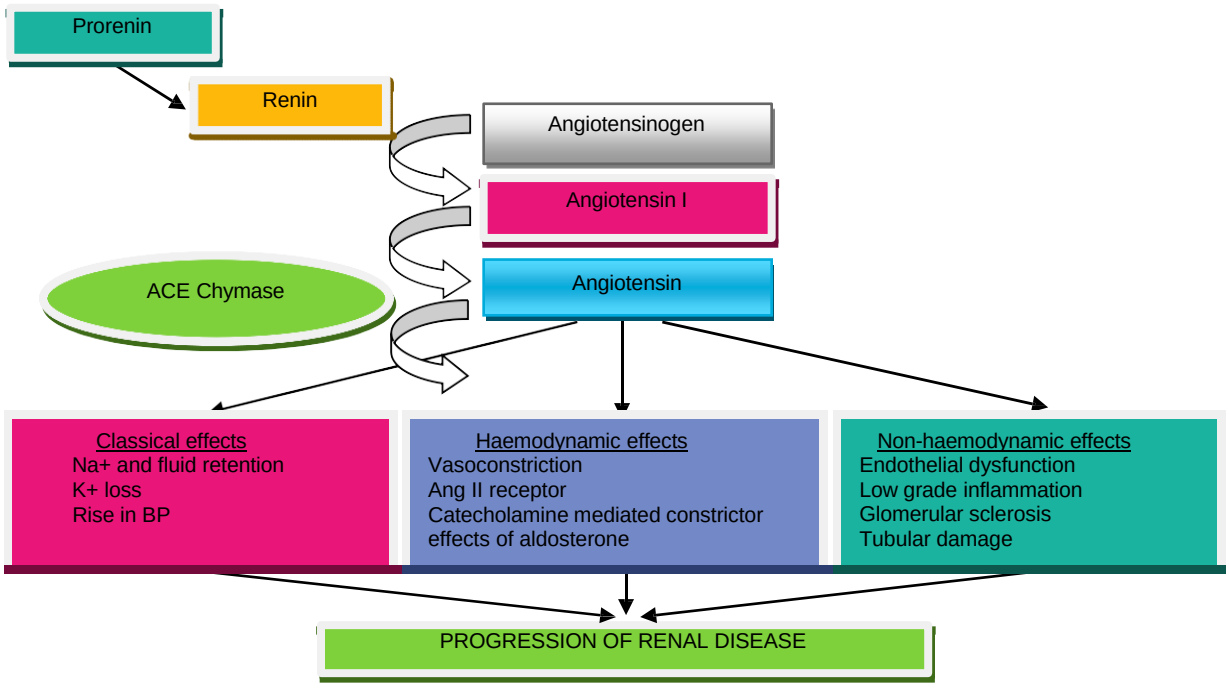

Figure 2: The Renin-Angiotensin-Aldosterone system (RAAS) in DN

9. ROLE OF ADVANCED GLYCATION END PRODUCTS IN DIABETIC NEPHROPATHY (AGEs)

Tissue protein glycation leads to initiation of diabetic nephropathy and other microvascular complications. In hyperglycemic conditions, excess amount of glucose binds to free amino acids on tissue proteins, which leads to non enzymatic reactions that result in reversible glycation products, and in a later stage in advanced glycation end products (AGEs), stable and long living molecules, which may be found in the circulation, and also in various tissues, including the kidney[26].

10. ROLE OF POLYOL PATHWAY IN DIABETIC NEPHROPATHY

Polyol pathway leads to initiation of diabetic nephropathy. The polyol pathway mainly consists of two enzymes namely, Aldose Reductase (AR), which leads to reduction of glucose to sorbitol with its co-factor (NADPH), and second enzyme is sorbitol dehydrogenase (SDH), with its co-factor NAD+, that converts sorbitol to fructose, a process that stimulate the ratio of NADH/NAD and result in activation of both oxidative stress and activation of protein kinase C[27].

11. ROLE OF PROTEIN KINASE C IN DIABETIC NEPHROPATHY

Stimulation of Protein kinase C plays an important role in diabetic nephropathy. Protein kinase C is divided into the eleven isoforms. Out of them nine protein kinase C (PKCs) are activated by the di acyl glycerol (DAG,) that is formed from excess glyceraldehyde- 3-phosphate. High glucose concentration results in increase amount of DAG, which leads to activation of protein kinase C. Protein kinase C activation then changes in renal blood flow[28], by decreasing production of Nitric Oxide[29], mesangial expansion, albuminuria and increases glomerular filtration rate (GFR), increases pro-inflammatory gene expression and vascular permeability in several models of experimental diabetes[30].

12. ROLE OF REACTIVE OXYGEN SPECIES IN DIABETIC NEPHROPATHY:

High glucose stimulates reactive oxygen species (ROS) in tubular epithelial cells and mesangial cells. Angiotensin-II activate reactive oxygen species (ROS) generation and amplifies many signalling pathways in diabetic kidney disease[31]. Increased reactive oxygen species (ROS) plays an important role in the development of diabetic nephropathy. Reactive oxygen species (ROS) mainly activate all of the important pathogenetic mechanisms, such as increased glucose entry into the polyol pathway, protein kinase C activation and increased production of advanced glycation end products (AGEs)[32].

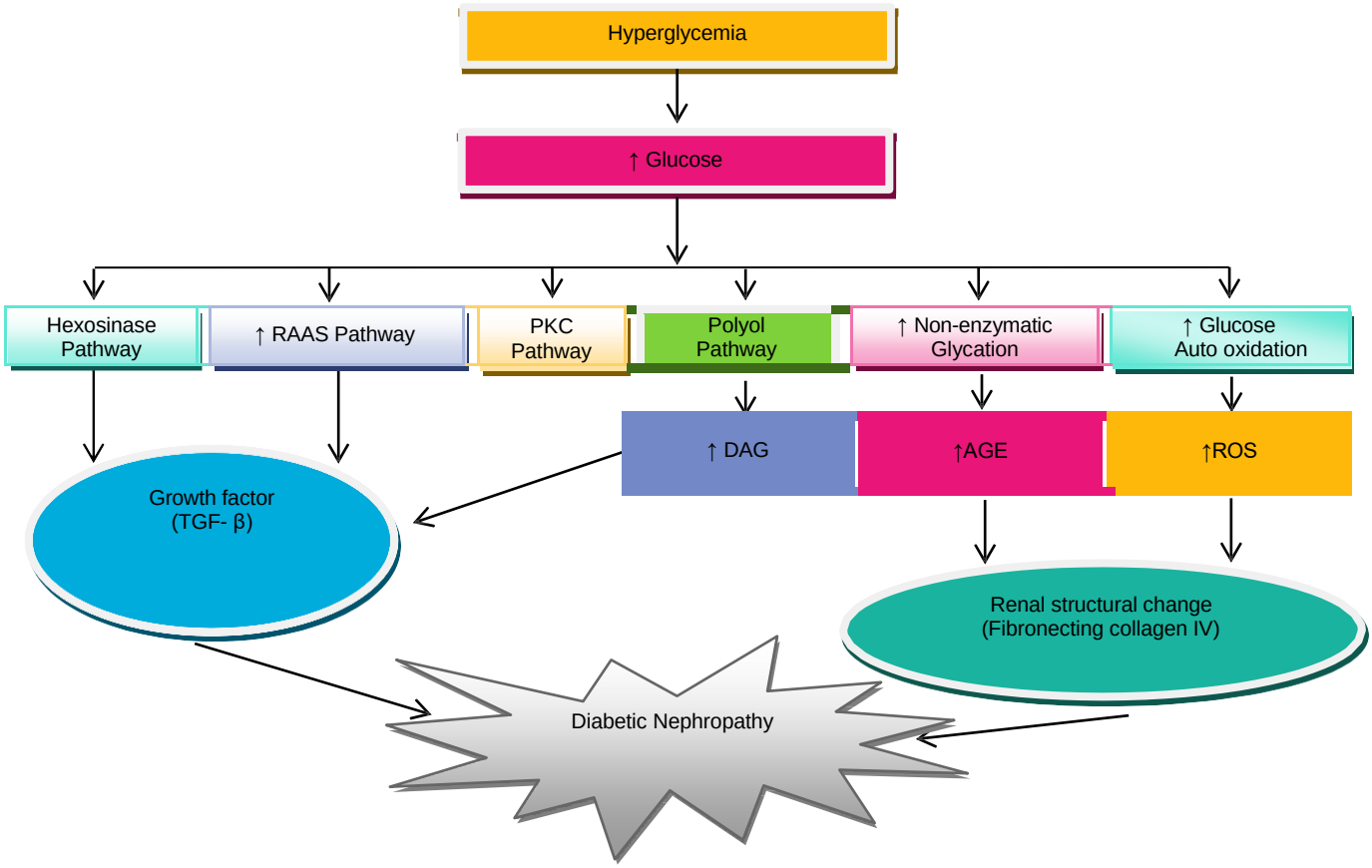

Figure 3: Pathways involved in pathophysiology of diabetic nephropathy

13. THERAPEUTIC MANAGEMENT IN DIABETIC NEPHROPATHY

Management of the diabetic nephropathy in patients must be therefore main focus on all cardiovascular risk factors as well as specifically on measures for retard the progression of end stage renal disease.

14. THERAPEUTIC MANAGEMENT OF DIABETIC NEPHROPATHY BY CONTROLLING PROTEIN INTAKE

A protein-restricted diet may help to delay the reduction in renal function. The intake of protein is 0.8–1.0 g/kg/ day in patients with macroalbuminuria (Urine albumin excretion >300 mg Creatinine/24 hr.), and 0.8 g/kg/day in the later stages of chronic kidney disease (CKD) help in the improvement of urine albumin excretion rate[33].

15. THERAPEUTIC MANAGEMENT OF DIABETIC NEPHROPATHY BY CONTROLLING GLYCEMIC CONTROL

A good glycaemic control has been shown to delay the progression of diabetes-related microvascular complications. Complications Trial Research Group and The Diabetes Control[34] and UK Prospective Diabetes Study Group reported that tight glycemic control can delay the progression of microvascular complications[35].

16. THERAPEUTIC MANAGEMENT OF DIABETIC NEPHROPATHY BY CONTROLLING CHOLESTEROL CONTROL

Dyslipidemia is the main risk factor for development of diabetic nephropathy. During diabetic nephropathy, triglycerides and cholesterol levels are increased. Better glycaemic control also shown to lowering the hyperlipidaemia levels[36].

17. THERAPEUTIC MANAGEMENT OF DIABETIC NEPHROPATHY BY CONTROLLING BLOOD PRESSURE CONTROL

Both of systolic and diastolic hypertension increasing the progression of diabetic nephropathy; so, the treatment of hypertension aggressively may be helpful in slowing the progression of nephropathy. Large prospective randomized studies in diabetes have demonstrated that maintaining a lower blood pressure (BP) (<140 mmHg) using ACE inhibitors provides an added benefit over other antihypertensive agents in delaying the progression of diabetic nephropathy[37].

18. TREATMENT OPTIONS FOR DIABETIC NEPHROPATHY

Based on pathogenesis of diabetic nephropathy, the initial pharmacotherapeutic treatment of diabetic nephropathy should be better control on hyperglycemia, dyslipidemia, proteinuria, hypertension, obesity, control of smoking, and restriction of protein intake. Patients who develop end stage renal disease will require renal replacement therapy. So the current use of angiotensin-converting-enzyme (ACE) Inhibitors found to be the most effective therapy in treatment of diabetic nephropathy[38].

19. ANGIOTENSIN-CONVERTING-ENZYME (ACE) INHIBITORS

Angiotensin-converting-enzyme (ACE) inhibitors are one of the most active classes of pharmaceutical drugs that are used primarily for the treatment of hypertension and congestive heart failure; they block the conversion of angiotensin I into angiotensin II[39]. According to the General Medical Services (GMS) the annual expenditure on angiotensin-converting-enzyme (ACE) inhibitors under the scheme exceeds an estimated $15 million. Angiotensin-converting-enzyme (ACE) Inhibitors has been widely approved for the treatment of diabetic nephropathy, coronary artery disease, hypertension and congestive heart failure [40]. Many different ACE inhibitors have been marketed. They differ from each other in regard to their potency, tissue affinity, chemical structure and pharmacokinetics etc. Its high lipophilicity is one of its main important character. This lipophilicity is useful in determination of various biological properties, such as an appreciable degree of biliary excretion, oral absorption, and probably more importantly, an increased tissue penetration.

With early diagnosis and treatment, use of Angiotensin-converting-enzyme (ACE) inhibitors help in delaying the progression of nephropathy in patients with microalbuminuria[41-42]. Until recently, treatment guidelines therefore recommended that angiotensin-converting enzyme (ACE) inhibitors are the first-line therapy for treatment of diabetic nephropathy in patients [43].

20. CLASSIFICATION OF ANGIOTENSIN – CONVERTING ENZYME (ACE) INHIBITORS

Based on the point of view of pharmacology, angiotensin-converting enzyme (ACE) inhibitors can be categorized into the following:

Captopril (Active drug), Alacepril, Moveltipril, Zofenopril, Ramipril, Lisinopril, Enalapril, Benazepril, Perindopril, Quinapril, Cilazapril, Spirapril, Delapril and Fosinopril.

All of the five newer angiotensin-converting enzyme (ACE) inhibitors (Trandolapril, Moexipril, Spirapril, Temocapril and Imidapril) are characterised by having a carboxyl functional groups and requiring hepatic activation to form pharmacologically active metabolites [44].

21. ROLE OF VARIOUS SYNTHETIC ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS IN DIABETIC NEPHROPATHY

21.1 Captopril

Captopril is the first angiotensin-converting enzyme (ACE) inhibitors which are used in clinical trials. The main mechanism of action of captopril in diabetic nephropathy is on renin, and aldosterone pathway[45]. Captopril treatment leads to decrease the levels of albuminuria and serum creatinine. Decline in GFR (glomerular filtration rate) occurs with treatment of captopril[46]. In diabetic nephropathy Captopril treatment leads to decrease in parameters of renal oxidative stress like reduction of inflammation and cell injury and decrease markers of tubulo interstitial injury[47]. Production of cytokine in endothelial nitric oxide synthase (eNOS) and renal macrophage infiltration in endothelial nitric oxide synthase (eNOS) is also reduced by Captopril treatment during nephropathy[48].

21.2 Enalapril

Enalapril is one of the most effective angiotensin-converting enzyme (ACE) inhibitor. It is poorly absorbed orally. It is suitable only for intravenous administration[49]. Protein kinase C and transforming growth factor β1 (TGFβ1) are the main targets of enalapril in nephropathy[50]. Treatment with Enalapril leads to decrease in levels of urine albumin excretion (UAE) and serum creatinine level in case of diabetic nephropathy[51].

21.3 Lisinopril

Lisinopril (lye-SIN-o-pril) is the lysine analog of enalapril. Lisinopril has a long duration of action. Historically, lisinopril was the third angiotensin-converting enzyme (ACE) inhibitor, after captopril and enalapril. It mainly inhibits the renin angiotensin aldosterone system (RAAS) pathway and transforming growth factor β1[52]. It has a number of properties that shows how it is better than the other angiotensin-converting enzyme (ACE) inhibitors[44]. The drug is useful in treating diabetic nephropathy by decreasing the levels of proteinuria, lowering the serum creatinine clearance thus improves the renal function [52].

21.4 Perindopril

Perindopril is also a long acting angiotensin-converting enzyme (ACE) inhibitor which has the slow onset of action. Perindopril mainly inhibits the renin angiotensin aldosterone pathway (RAAS) in nephropathy. Because perindopril is widely used in the practice of clinical trials, it may represent an effective new therapy for anticancer[53]. The drug is useful in treatment of diabetic nephropathy, shows significant improvement in the signs and symptoms of diabetic nephropathy by lowering the levels of BUN (blood uria nitrogen), Albuminuria, serum creatinine. Histopathological study shows that the drug is also effective in decreasing the progression of glomerular hypertrophy[54].

21.5 Ramipril

Ramipril is an active prodrug. Like enalapril, ramipril also possesses high lipophilic property and long duration of action. The renin-angiotensin- aldosterone system (RAAS), which is one of the most important elements of the regulation of blood pressure that have an important role in the development of diabetic nephropathy[55]. Apart from its blood pressure decreasing effect, ramipril protects the target organs and proved to be effective in the treatment of diabetic nephropathy according to the most international multicenter clinical trials[56]. The drug is useful in treatment of diabetic nephropathy by decreasing the albuminuria level thus restored the glomerular nephrin expression [57].

21.6 Benazepril

Benazepril is a non sulfhydryl angiotensin-converting enzyme (ACE) inhibitor that is used in patients with mild to moderate hypertension. It is also effective for patients with congestive heart failure & also leads to decrease in systemic & pulmonary resistance. The drug is mostly useful in geriatric patients[58]. Renoprotective effect of benazepril in nephropathy is mainly related to the inhibition of angiotensin II MAPK (mitogen activated protein kinase) pathway. Benazepril treatment in diabetic nephropathy is useful in reduction of proteinuria level thus improving the renal hypertrophy[59].

21.7 Quinapril

Quinapril is a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. It is intermediate acting angiotensin-converting enzyme (ACE) inhibitor which has a shorter half-life[60]. In nephropathy quinapril mainly inhibits elevated lipid peroxidation level. In diabetic nephropathy, Quinapril is effective in diabetic nephropathy by decreasing the urine albumin excretion (UAE) level by affecting the fibronectin protein accumulation in glomeruli [61].

21.8 Cilazapril

Cilazapril is a new angiotensin-converting enzyme (ACE) inhibitor useful in the management of mild to moderate hypertension. It is orally administered prodrug. It has a long duration of action[62]. Cilazapril suppress the transforming growth factor β1 (TGFβ1) in diabetic nephropathy. In nephropathy, the drug is useful in prevention of glomerular hypertrophy[63].

21.9 Zofenopril

Zofenopril are the angiotensin-converting enzyme (ACE) inhibitor with sulphydryl groups (SH) and consequent potential antioxidant activity which has been shown to have beneficial effects in hypertension and diabetic nephropathy. Renin angiotensin aldosterone system (RAAS) is the main target which is involved in diabetic nephropathy[64]. This drug is useful in treatment of diabetic nephropathy by decreasing the levels of proteinuria, serum creatinine, urine albumin excretion (UAE), and BUN (blood uria nitrogen)[65-73].

21.10 Fosinopril

Fosinopril is a new generation of phosphinic acid angiotensin-converting enzyme (ACE) inhibitor that is indicated for the treatment of hypertension in a dose once daily[66,74-78]. Fosinopril inhibits the lipid peroxidation level in nephropathy. Fosinopril is useful in treatment of diabetic nephropathy by lowering the levels of cholesterol, proteinuria, serum creatinine and urine albumin excretion levels[67,79-84].

21.11 Imidapril

Imidapril hydrochloride (Imidapril) is a non-sulfhydryl, long-acting, angiotensin-converting enzyme (ACE) inhibitor. Clinically this drug is used in the treatment of hypertension, chronic congestive heart failure (CHF), diabetic nephropathy and acute myocardial infarction (AMI)[68,85-90]. Receptor associated prorenin system (RAPS) is the target involved in nephropathy. The drug is effective in treatment of diabetic nephropathy thus preventing the glomerular injury[69,91].

21.12 Alacepril

The drug is useful in treatment of diabetic nephropathy, by reducing the levels of urine albumin excretion (UAE), serum total cholesterol[70]. Malondialdehyde (MDA) level is inhibited by the treatment with alacepril. Alacepril is also effective in reduction of renin angiotensin aldosterone system (RAAS) pathway which is elevated in the diabetic nephropathy[71,92-96].

21.13 Delapril

Delapril is an angiotensin-converting enzyme (ACE) inhibitor which is most widely used in treatment of diabetic nephropathy. Delapril shows significant reduction in the GFR (glomerular filtration rate) Delapril is more effective than the other angiotensin-converting enzyme (ACE) inhibitors[72,97,98].

21.14 Moxepril

It is an angiotensin-converting enzyme (ACE) inhibitor which is used in the treatment of diabetic nephropathy by reducing of the parameters that is elevated in diabetic nephropathy, like reduction of aldosterone and serum creatinine thus improves the renal fibrosis. Moexipril mainly inhibits the two pathways renin angiotensin aldosterone system (RAAS) and transforming growth factor β1 (TGFβ1) in nephropathy. Moexipril treatment also leads to reduction of the urine protein level[73,99-102].

21.15 Trandolapril

Trandolapril is well known angiotensin converting enzyme (ACE) inhibitor with many cardiovascular (CV) indications. Trandolapril in nephropathy mainly suppress the transforming growth factor β1 (TGF-β1) and tumor necrosis factor α (TNF-α). In diabetic nephropathy, trandolapril treatment reducing the progression of proteinuria and also effective in reduction of inflammation or interstitial fibrosis in high-risk patients[74].

Table 1: List of commonly used angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB's)

S. No.	Author	Name of drug (ACE inhibitor)	Conclusion
1	Akbar *etal.,*2012 (45)	Captopril	Captopril lowers the albumin excretion levels, renal, tubular and glomerular hypertrophy.
2	Xu *et al.,* 2013 (50)	Enalapril	Enalapril was found to be effective in Preventing harmful effects of diabetic nephropathy.
3	Jin *et al.,* 2014 (75)	Benazepril	Benazepril are useful in treatment of diabetic nephropathy by suppressing the expression of TGF beta R.
4	Trujacanec *et al.,* 2013 (54)	Perindopril	Perindopril was found to be more effective in prevention of BUN, UAE, serum creatinine and renal corpuscle damage in diabetic nephropathy.
5	Rao *et al.,* 2011 (76)	Trandolapril	Combination therapy of Trandolapril and telmisartan was found to be more effective in diabetic nephropathy.
6	Castoldi *et al.,* 2013 (57)	Ramipril	Ramipril reduces the proteinuria, Albuminuria levels and restored glomerular nephrin expression in diabetic nephropathy.
7	Watson *et al.,* 2012 (61)	Quinapril	Quinapril decrease the proteinuria, UAE level in treatment of diabetic nephropathy.
8	Kojima *et al.,* 2013 (77)	Lisinopril	Lisinopril normalized the level of GFR during nephropathy.
9	Mohamed *et al.,* 2013 (73)	Moexipril	Moexipril lowered the urinary protein excretion, serum creatinine, aldosterone levels and glomerular injury in diabetic nephropathy.
10	Ichihara *et al.,* 2006 (69)	Imidapril	Imidapril reduced the urinary albumin excretion and improved the glomerulosclerosis in nephropathy.
11	Zhang *et al.,* 2006 (78)	Fosinopril	Fosinopril reduced the urine protein excretion, lowers the blood glucose level and serum creatinine levels in type 2 diabetic nephropathy.

22. IMPORTANCE OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS OVER OTHER DRUGS USED IN DIABETIC NEPHROPATHY

For many years the benefit of low-dose treatment with angiotensin converting enzyme (ACE) inhibitors is increasing because angiotensin converting enzyme (ACE) inhibitors leads to prevention or delay the complications of diabetic nephropathy[79]. This therapy is an important element of a combined aggressive approach which shows effectively or significantly reduction of cardiovascular mortality and also in type 2 diabetic nephropathy[80]. The most important advantages of angiotensin converting enzyme (ACE) inhibitors over other classes are, for the cardiorenal end points in patients suffering from diabetes[81]. Consequently, the current medical opinion suggested that patients suffering from diabetes and its complication like microalbuminuria should be treated with the angiotensin converting enzyme (ACE) inhibitors as per guidelines of the National Kidney Foundation Algorithm. The use of angiotensin converting enzyme (ACE) inhibitors produce statistically significant reductions in albuminuria. Stratification reduces the heterogeneity and supports treatment with angiotensin converting enzyme (ACE) inhibitors is to reduce the progression of nephropathy in patients with type 2 diabetes mellitus. Until recently, angiotensin converting enzyme (ACE) inhibitors were considered first-line therapy for treatment of diabetic nephropathy[82].

23. CONCLUSION

Individuals with diabetes are prone to many other complications, both acute and chronic. The diabetic complications results in more hospitalizations, disability, and death[83]. Due to the excess of diabetic patients, the morbidity and mortality rates are high particularly of those persons who are suffering from nephropathy, and the more amount of money spent in dialysis and renal transplantation, that shows that the present huge socioeconomic burden of diabetes may results in exponentially increases[84].

The effect of different kinds of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are studied by the multiple study experiments either as monotherapy and with combination, also these are useful in demonstrating the

effectiveness of both classes of agents in lowering blood pressure and reducing both cardiovascular mortality and morbidity in various high risk populations of patient, including the patients suffering with type 2 diabetes [85].

24. FUTURE DIRECTIONS

This review focused on the pharmacology of angiotensin converting enzyme (ACE) inhibitors and on the broadening clinical applications of this class of compounds. Clearly, the beneficial cardiovascular and renal effects of angiotensin converting enzyme (ACE) inhibitors is effective for the treatment of diabetic nephropathy. Although current clinical efforts are directed at the emerging role of angiotensin converting enzyme (ACE) inhibitors in preventing cardiovascular events in normal subjects, further work needs to be done to characterize molecular and cellular mechanisms responsible for the clinical effects of angiotensin converting enzyme (ACE) inhibitors. It is clear that angiotensin converting enzyme (ACE) inhibitors represent one of the major advances in cardiovascular therapeutics over the past 20 years. Furthermore, angiotensin converting enzyme (ACE) inhibitors, in very short terms, are useful in treatment of diabetic nephropathy[86].

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