A review on the therapeutic approach to the Diabetic Nephropathy

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Abstract

Diabetes mellitus leads to a number of secondary complications and diabetic nephropathy is one of the most complicated abnormality of DM with the huge rate of morbidity and mortality and it is also the leading cause of ESRD in adults. The link between glycemia level and development of hypertension has been proved through landmark follow up by DCCT, according to that on 8th year of follow up there was 10% decline in development of hypertension in intensified insulin regimen treatment group as compare to the conventionally treated group. The most important etiology behind the occurrence of diabetic nephropathy in both classes of diabetics are due to high glucose level in the body. According to several research groups including the Diabetic Control and Complication Trail, intensified glycemic control can prevent the incidence and development of microalbuminuria and also overt proteinuria in type 1 diabetic patients. There are a number of therapeutic strategies has been used for the diabetic nephropathy managements, but still we are in search of a drug with better efficacy and having less side effects. Phytochemical and medicinal plants based drugs could be a novel one, which need to be properly evaluated for their efficacy and bioavailability.

Keyword: *Nephropathy; insulin; diabetes; ACE inhibitors; protein kinase*

Introduction

Diabetes mellitus leads to a number of secondary complications and diabetic nephropathy is one of the most complicated abnormality of DM with the huge rate of morbidity and mortality and it is also the leading cause of ESRD in adults. [1]. About 30% of diabetic patient (either type1 diabetes mellitus or type 2 diabetes mellitus) develops diabetic nephropathy [2] and in the case of poorcontrol of blood pressure and urinary albumin excretion, they lead to ESRD about 80% of which have hypertension which contributes in worsening of renal disease [3]. In DM type 2 hypertension is the part of syndrome characterized by insulin resistance, hyperuremia, dyslipidemia, obesity and atherosclerosis [4] though the exact cause and explanation of condition is still unknown but according to many researchers. Insulin resistance plays important role in the development of syndrome [5], but in the case

of DM type 1 hypertension develops secondary to the occurrence of DN [6]. The link between glycemia level and development of hypertension has been proved through landmark follow up by DCCT (Diabetes Control and Complication Trail), according to that on 8th year of follow up there was 10% decline in development of hypertension in intensified insulin regimen treatment group as compare to the conventionally treated group. Likewise there were beneficial effects on renal consequences of first group [5].

Therapeutic approach to DN:

By getting deep information about the mechanisms of development and pathogenesis of diabetic nephropathy scientist are trying either to decrease the level of causative agents or block the leading pathways toward diabetic nephropathy. And thus the main therapeutic agents and strategies are suggested as follows.

Table 1: Mechanisms for therapy of DN

Mechanism	Treatment
Metabolic	
✓ Hyperglycemia	Insulin
✓ Increase glucose derived protein	Aminoguanidine, AGE cross link breakers
✓ Polyol pathway	Aldose reductase inhibitors
Mechanical/Hormonal	
✓ Elevated systemic blood pressure	Anti- hypertensive drug
✓ Increased intraglomerular pressure	ACE inhibition, lower protein diet
✓ Increased vasoactive hormones	ACE inhibition, Angiotensin VI antagonist ET receptor antagonist
Intermediate pathways	
✓ Growth factors eg: TGFβ, TGF	Antibodies
✓ Protein kinase C dependent	PKC β inhibitors

Glycemic control

Hyperglycemia is considered as a major cause of development of diabetic nephropathy in both type 1 and type 2 diabetic patients [7]. According to several research groups including the Diabetic Control and Complication Trail, intensified glycemic control can prevent the incidence and development of microalbuminuria and also overt proteinuria in type 1 diabetic patients [8]. The 6 year study done by Ohkubo et al 1995 in Japanese patient with

type 2 DM, multiple insulin therapy showed marked decrease in development of diabetic nephropathy [7] Diabetic Control and Complication Trail (DCCT) has suggested that by controlling intensively glycemic level(goal HbA1c< 6.5% and mean achieved Hb≈7%) in both type 1 and type 2 diabetic patients marked reduction in the development of micro-vascular complications like retinopathy, nephropathy and neuropathy is seen [9]. In UK, a 10 year study was done on the newly diagnosed patients with type 2 DM, in whom the intensified glycemic control, showed a 25% decrease in the rate of progression and development of secondary diabetic complications as compare to standard therapy. Study which was done by Vijan S *et al.* 1997 showed that glycemic control in type 2 DM is more beneficial in prevention of development of secondary complications than in type 1 DM [7]. However some controversial studies are also present like according to the research done by DCCT and Micro albuminuria study group, intensified blood glucose control was not able to decrease the rate of progression from microalbuminuria to macroalbumiuria in type 1 diabetic patients [8, 10]. But glycemic control along with blood pressure control in type 1 diabetic patients was reported to prevent the worsening of renal function [11].

In type 2 diabetic patient, the role of strict glycemic control is less studied but there are reports on some hypoglycemic agents for example Rosiglitazone is reported beneficial in decreasing the UAE rate as compare to the Glyburide [12]. Use of metformin due to the risk of lactic acidosis is inhibited in patients with high level of creatinine [9] in these patients use of drugs independent from renal excretion are safe, for example Repaglinide and Nataglinide but Sulfonuria and its derivatives will worsen the condition [13]. However, in the study for type 2 diabetic patients with exogenous insulin should be administered because of low production of endogenous insulin in response to insulin secretagogues [9].

Intensive blood pressure control

Hypertension is a common problem of diabetic patients; about 40% of type 1 and 70% of type 2 diabetic patients are with normo-albumiuria [14] thus the hypotensive agents are reported to significantly decrease the risk of development of micro and macro vascular complications [9]. The study in UKPDs has shown that a decrease of 10mmHg (from 154 to 144 mmHg) reduces the risk of development of DN to 29%. As hypertension is consider critical to renal function so control of blood pressure with any of hypotensive agent may be beneficial [15] but RAS blockers either ACE inhibitors or ARBs despite of their anti-hypertensive characteristics are preferred due to the role of this system in the pathogenesis of diabetic nephropathy and their effect in decreasing intraglumerular pressure that results little passage of proteins to proximal tubules [16].

Though the preventive effects of ACE inhibitors has not been defined yet but a 3 year study in normotensive, normo-albuminuric type 1 diabetes showed delay in progression of DN about 24% in type 2 diabetic patients and also Ramipril was reported to decrease the urinary albumin excretion rate, thus ACE inhibitors can be beneficial agents in prevention of developing DN [9]. The meta-analysis of evaluation of 12 trails containing 698 non-hypertensive type 1 diabetic patients showed ACE inhibitors are not only beneficial in decreasing the chance of progression from micro-albuminuria to macro-albuminuria but they are also beneficial in increasing the chances of regression from micro-albuminuria to normo-albumiuria [17]. Furthermore, ARBs are proved to be efficient in prevention of the development of micro-albuminuria to macro- albuminuria in type 2 diabetic patients, treated with Irbastan 300mg/dl which showed a 70% decrease in development of diabetic nephropathy [18].

Novel therapy

(a) ***Strategies to block AGE formation:*** The AGE can be blocked by several pathways. Most of therapeutic strategies till now, work on the inhibition of synthesis of AGEs. Aminoguanidine is the most studied AGE blocker; it is a nucleophilic compound by interacting with the intermediates of AGEs inhibits the process of cross linking [19]. The studies done in diabetic animal model have shown the efficacy of aminoguanidine in the attenuation of the signal transduction, over expression of growth factor, structural and functional alteration of diabetic nephropathy [20]. The study done by Ateon a pharmaceutical company responsible for this research has concluded the significant reduction in the albuminuria following the administrating of aminoguanidine [21]. But there was no statistical significant change in GFR level. Some other AGE inhibitors that require further studies for clinical use are ALT 486, NNC 39-0028 and OPB 9195 Cross link breakers: other proposed strategy of therapy is the breaking of cross linking, the idea was developed when phenacylthiazolium(PBT) a cross link breakers was discovered [22]. But the study conducted on diabetic rats did not proved the efficacy of PBT in the treatment of DN. Another cross link breaker is ALT 711 which is able to inhibit and also to improve age related stiffness of myocardium and has also been shown to significantly beneficial to reduce blood pressure, UAE and renal lesions [23].

(b) ***Receptor blocker:*** Shmidt and collegues suggested another therapeutic strategy by administration of soluble, extracellular domain of RAGE (sRAGE) that was able to bind with AGE and thus inhibiting its receptor, subsequent gene activation and underlying pathophysiology [24].

(c) ***Protein kinase C inhibitors:*** As the number of pathogenic pathways toward DN is activated by PKC the

inhibition of PKC can be efficient therapeutic strategy in the management of DN on other side there are several isoforms of enzyme performing different function, therefore while inhibiting the specific isozyme related induction of DN (PKC-β) should be targeted [25].Inhibitors of PKCβ ameliorate glomerular lesions thus normalize GFR and inhibit protein excretion in diabetic rat models [26]. Till now the known inhibitor of PKC is LY333531 that was able to reduce UAE and GFR in diabetic rat models. That also resulted in attenuation of mesangial expansion, reduction of collagen and expression TGF-β expression in Ren-2 diabetic rats, even in the presence of hyperglycemia.

(d) ***Inhibition of vasopeptidase:*** The important vasopeptidases that contribute to the control of blood pressure are RAS, Kalikarin-Kinin system and natriuretic peptide system. All of these systems together play role in modulating the vascular tone, water and salt balance and have growth factor like activity. Interrelation of these systems is also important in the development of hypertension and renal complication. ACE and neutral endopeptidase have structural similarities and both are zinc containing cell surface peptidases therefore can be inhibited by single inhibitor. The inhibition of both systems can lead to better control of blood pressure. Furthermore, other vasoactive peptidases are also reported to be affected by changes in these systems. For example the degradation of bradykinin is inhibited by ACE inhibitors and NEP inhibitors reduce the endothelin and potentiate the natriuretic effect of adrenomedullin [25]. Several preclinical and clinical studies are going on dual ACE/NEP vasopeptide inhibitors like Omapatriate the phase II and III studies for which are completed [27]. SA7060, MLD100240, MLD100173, Fasidotril, Sampatrilat, Alanopril, CGS30440 and S21402 [28]. Number of studies are done on animal models to evaluate the comparative action of dual VPIs and ACE inhibitors. In one study the S21402 dual VPIs was compared with ACE inhibitors and in result the S21402 was found more efficient in controlling of blood pressure while the effect on AER was similar [29]. The other study was done on semi nephrectomized mice with some characteristics of DN, to study the effects of CGS 30440 and Omaptrilate, both of these VPIs were able to significantly reduce proteinuria [30].

(e) ***Miscellaneous therapeutic strategies:*** Overdose of thiamin and its derivative Benfothiamin due to decrease oxidative stress, PKC and protein glycation is reported to slow down the development of microalbuminuria in diabetic nephropathy [31]. The administration of heparin glycosaminoglycan apart from the beneficial effects of PKC inhibitors also decrease the accumulation of tubular and glomerular matrix and inhibit the synthesis of PKC mRNA [30]. Pimagedine a second generation of AGE inhibitor and Suldexide a

glycose amino glycan also have beneficial effects in the decreasing of the urinary albumin excretion and in normalization of GFR in diabetic rat models. Taniguchi K *et al* 2013 suggest the role of Src kinase in collagen accumulation and PP2 by inhibition of Src kinase that leads to the inhibition of collagen IV accumulation, high glucose induced phosphorylation of proteins and the pathological mechanisms of diabetic nephropathy thus Src inhibitors were suggested as a novel therapeutic targets for diabetic nephropathy [31].

Role of PG in the pathogenesis and development of DN is not clear but there is higher amount of PG in the kidney of patient and also diabetic animal models with diabetic nephropathy. Makino *et al* 2002 showed that administration of selective antagonists of PGE receptor EP-1 subtype was able to selectively prevent development of diabetic nephropathy in STZ induced diabetic rats, Which was able to decrease massengial expansion, ameliorate glomerular hypertrophy, inhibit up regulation of fibronectine and transcriptional growth factor β1 (TGF-β1) in messengia cells cultured in high glucose concentration. According to this study the role of PG-EP1 system in the development of diabetic nephropathy become clear. Makino *et al* 2002 also explained that aspirin a non - selective prostaglandin synthase inhibitor and EP-1 antagonist both decreases messengial expansion but aspirine is not able to inhibit glumerular hypertrophy and proteinuria while EP-1 inhibitor is able to produce these changes suggesting that the mode of action of these drugs may be different and suggests the novel therapeutic strategy [32]. Studies conducted on STZ induced diabetic rat models have suggested that in renal mitochondria high level of SO is produced along with the post transcriptional modification of mitochondrial compexIII. Thus Chacko BK *et al* revealed out that in $Ins2^{+/\_AKitaJ}$ mice targeted antioxidant therapy with mitochondria –targeted ubiquinone (Mito Q) was able to prevent and treat diabetic nephropathy [33]. However the studies in human being are still needed to approve the effect of these novel drugs.

Herbal therapeutic agents:

Since ancient years medical plants play an important role in the treatment and prevention of disease. For the treatment of diabetes mellitus and for prevention of occurrence of diabetic induced secondary micro and macro vascular complication certain medical plants are known. That contributes not only at therapeutic level side by side with pharmacological medicines also helps financially diabetic patient because of low cost and ease of use. Well-known plants containing antidiabetic characteristics that were approved as hypoglycemic agents by

researchers were listed by Bnouham M *et al* (2006) [34]. They are *Momordica charantic L, Ficus bengalensis L, Polygala seneg L, Gymnema sylvestre R, Opuntia streptocautia Lem, Alium sativum, Aloe, Artemisia*. A list of Indian medicinal plants owing antidiabetic activity was proposed by Modak *et al*. 2006 containing *Allium sativum, Trigonella foenum graecum, Tinospora cordifolia, Eugenia jambotana, Pterocarpus marsupium, Withiana somnifera, Phyllanthus armus, Momordica charanhia Ocimum sanctum, Camella sinenses* [35].

Conclusion

According to several research groups including the Diabetic Control and Complication Trail, intensified glycemic control can prevent the incidence and development of microalbuminuria and also overt proteinuria in type 1 diabetic patients. Hypertension is a common problem of diabetic patients; about 40% of type 1 and 70% of type 2 diabetic patients are with normo-albumiuria [25] thus the hypotensive agents are reported to significantly decrease the risk of development of micro and macro vascular complications. There are a number of therapeutic strategies has been used for the diabetic nephropathy managements such as Insulin, Aminoguanidine, AGE cross link breakers Aldose reductase inhibitors, Anti- hypertensive drug, ACE inhibition, lower protein diet, Angiotensin VI antagonist ET receptor antagonist, protein Kinase C inhibitors, But still we are in search of a drug with better efficacy and having less side effects. Phytochemical and medicinal plants based drugs could be a novel one, which need to be properly evaluated for their efficacy and bioavailability.

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