Diabetic nephropathy and its therapeutic options: A Review

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Abstract: **Diabetic nephropathy (DN) or diabetic kidney disease means the degeneration of kidney function which can be seen in chronic type 1 and type 2 diabetes mellitus patients. Diabetic nephropathy is the leading cause of chronic renal disease and a major cause of cardiovascular mortality. The development of the disease is known to occur in different type stages and is connected to glycemic and blood pressure control. Although, despite aggressive blood sugar control the prevalence of chronic kidney disease (CKD) I in diabetic people have not been seen in the last two decades: which has now lead to the recognition of new additional factors in the development. The two main risk factors for diabetic nephropathy are hyperglycemia and arterial hypertension, but the genetic susceptibility in both type 1 and type 2 diabetes is of great importance. Other risk factors are smoking, dyslipidemia, proteinuria, glomerular hyperfiltration, and dietary factors. The nutritional station of the patient is a very vital and changeable factor that may influence CKD procedure and the result. It directly comes from the traditional diet choices that the patient makes base on poor nutritional recognition. Dietary management of DN victims is challenging, as the factors of diet overload on the kidney function required to be maintained with malnutrition. The single best evidence-based therapy for diabetic nephropathy is therapy with a RAS-blocking medication. The introduction of antioxidant and anti-inflammatory agents to this field had also added a wealth of knowledge. However, many of these agents are still waiting for well-designed clinical studies to prove their beneficial therapeutic role.**

Keywords: **Diabetic Nephropathy(DN), renal disease, Nano formulation, Diabetes mellitus(DM)**

I. INTRODUCTION

A. Diabetic Nephropathy and diabetes

Kidney disease is associated with increased total mortality and cardiovascular morbimortality in the general population and patients with T2DM (Type 2 diabetes) [47]. The prevalence of DN varies according to ethnicity: it is much higher in African-Americans, Asians, and Native-Americans than in Caucasians. African-Brazilians are very more susceptible to progress to end-stage renal disease(ESRD) than people of European ancestry but they appear to be a similar prevalence of micro or macroalbuminuria [2]. Diabetic nephropathy becomes the main cause of end-stage renal failure in the western part of the world [14]. Part of the most important clinical factor of diabetes is connected to chronic tissue complications. Histological changes in DN are identical in T1DM and T2DM. People with T1DM (Type 1 diabetes) and T2DM have equivalent rates of proteinuria, azotemia and ultimately End-stage kidney disease (ESKD) [44]. This was then estimated to grow to almost 550 million people by the year 2035. [1] The early morphological signs of renal damage include nephromegaly and a modified Doppler, but the degree of damage is best ascertained from proteinuria and GFR (Glomerular filtration rate). The core function of the glomerulus is the GFB (Glomerular Filtration Barrier), which has the unique capacity to selectively filter molecules and proteins by size and charge, thus maintaining the body's electrolyte and pH balance and blood homeostasis. [31] Renal disease is a major cause of morbidity and mortality for a patient with insulin-independent diabetes mellitus (IDDM) and is now becoming an increasingly important clinical problem in Non-

insulin-dependent diabetes mellitus (NIDDM) [14]. A little term increase in hyperglycemia does not lead to serious clinical complications [1]. The complication was traditionally thought to result from the interaction between hemodynamic and metabolic factors [44, 48]. The time and severity of the increase in glucose level is the major causative feature in starting organ damage. The average occasion of diabetic nephropathy is higher as of the first 10 to 20 years after diabetic onset. It takes up to almost 15 years for the blood vessels in the organs like the eyes, kidney, and nerves to get influenced. [1] It was examined that almost more than 20 and up to 40% of the diabetic victims will generate Chronic kidney disease (CKD) but which is based on the population, with a very vital number that generates ESKD needing renal replacement therapies like kidney transplantation. Diabetes which has no clinical sign of kidney destruction during the initial 20 to 25 years is very importantly less likely to cause major renal complication in 4/24 the late period of a victim's life. [1] The Joint Committee on Diabetic Nephropathy has revised its Classification of Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) in line with the widespread use of key concepts, such as the eGFR and CKD. [18].
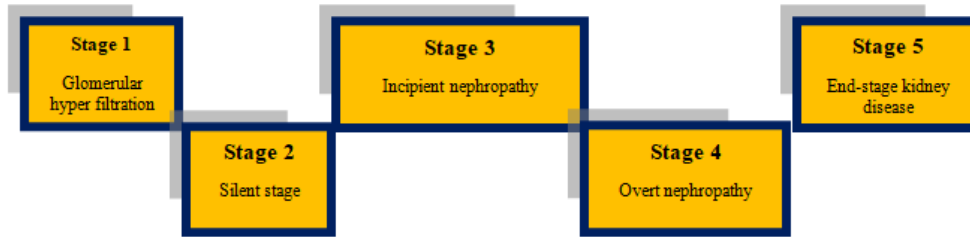
B. Stages of Diabetic Nephropathy

DN has been didactically categorized into stages according to the UAE values. The values used to characterize these stages are described in the table.1. [2]

Table 1: Diabetic nephropathy stages based on urinary albumin excretion

Stages	Urine with marked time *(µg/min)*	24 hours urine (mg/24h)	Random urine sample	
			Albumin conc (mg/l)	Albumin/creatinine Ratio(mg/g)
Normoalbuminuria	<20	<30	<17	<30
Microalbuminuria	20 --199	30 -- 299	17 -- 173	30 -- 299
Macroalbuminuria	≥ 200	≥ 300	≥174	≥300

The concept of kidney disease is based on the presence of albuminuria and/or impaired renal function that lasts for more than three months [47]. Moreover, albuminuria predicts an increased risk of myocardial infarction, stroke, cardiovascular (CV) death, total death, and heart failure in patients with T2DM in comparison with non-diabetic patients [47]. The relationship between the mechanisms responsible for the development of albuminuria and renal impairment is not clear [47, 11]. DN is characterized by microalbuminuria and macroalbuminuria, and morphological changes such as glomerular thickening, interstitial fibrosis, the formation of nodular glomerulosclerosis and decreased endothelial cell fenestration [48]. Microalbuminuria is referred to as the risk factor for the generation of macroalbuminuria but not all the victims advance to this particular stage and some may even regress to Normoalbuminuria.[17,2]. The first examination suggested that almost about 75 to 80% of type 1 diabetic victims with microalbuminuria would advance to proteinuria for over a period 6 of 14 years and up to date, the examination suggested that 30 to 45 % of the microalbuminuric victims will advance to proteinuria over 10 years follow up [2]. Some of them will present regression to normoalbuminuria and this can lead to a result of more intensive sugar and blood pressure (BP) control process employed within the late decades than within the first studies. The regression of the microalbuminuria is more often among patients with a short duration of microalbuminuria, glycohemoglobin A1C (HbA1c) below 8%, systolic BP >115mmHg, and favorable lipid profile. [4] Unrestrained of the role as a prognostic feature for macroalbuminuria, the looks of microalbuminuria, reflecting a stage of generalized endothelial dysfunction, could be a dangerous factor for heart disease and mortality. [2] As seen in the microalbuminuria stage, there is no expectation of GFR to decline. Once the patient has developed macroalbuminuria, the GFR is expected to decline to 1.2 ml/min/month in type 1 DM. But this could be decreased by BP treatment. IN type 2 DM, the rate of the GFR decline is unpredictable or less predictable.[2] A mean decline of almost 0.5 ml/min/month has been examined, but in some victims, GFR may remain stable for a very long period. However, the greater GFR decline is related to many advanced diabetic glomerulopathies and poor metabolic control. Hence the progress of kidney disorder can be explained in different stages which is given in fig.1. Extensive studies in the Western world have demonstrated that diabetic patients with microalbuminuria have an increased risk of progression to overt proteinuria, and after some time, renal failure [11]. Among the 1,478 patients with T2DM who had available data for calculating both GFR and albuminuria, patients with albuminuria without renal impairment and nonalbuminuric renal impairment were compared. The prevalence of albuminuria without renal impairment (albuminuria alone) (13.5%) and nonalbuminuric renal impairment (14.7%) was similar [47].

Figure.1. Different stages of nephropathy

c. *Cause/Risk Factor of DN*

Many epidemiological studies demonstrate that ethnicity, family history, gestational diabetes, elevated blood pressure, dyslipidemia, obesity, and insulin resistance are the major risk factors of diabetic nephropathy [49]. There are two most basic risk factors of DN and which are hyperglycemia and arterial hypertension (which is a pressure that is acting very importantly on the walls of the arteries). [1] After the studies, it was seen that even with the presence of hyperglycemia and also elevated BP for a very long period, DN develops only in about 40% of the patients. So this outcome raised the concept that DN will be generated only in a susceptible subset of victims [2] and based on the family studies, it was confirmed that a genetic factor will also contribute to the development of DN in both type 1 and type 2 DM. Once the DN occurs, the advancement factors may act, which may favor the evolution to more advanced stages. There is proof that some of these factors which are involved in the generation of proteinuria are also similar to the loss of GFR, but others are special to each one of them (Fig.2.). [2]

1. **Hyperglycemia**: It is known to be the minor reason or risk factor for the development of macroalbuminuria in both type 1 and type 2 DM. In the presence of micro and macroalbuminuria, the role of metabolic control is less defined, although some studies have verified the decrease of blood glucose on GFR. And it has been shown that the transplantation of the pancreas reverses renal damage in type 1 DM victims with mild to progressed DN lesions. A decrease of about 1% HbA1c with a 37% decrease in the microvascular endpoint. [1, 2, 7, 10]. Moreover, it was demonstrated that pancreas transplantation reversed renal damage in type 1 DM patients with mild to advanced DN lesions [7]. Recently a large trial also reinforced the importance of intensive treatment of DM to decrease the microvascular complications [10]. Hyperglycemia secondary to DN might induce major structural changes in the glomerulus, such as the thickening of the glomerular basement membrane, the impairment of glomerular cells within glomeruli [31].

2. **Arterial Hypertension:** It is the major or main reason for the development of DN and is also known to be the most relevant factor related to its progression. According to The United Kingdom Prospective Diabetes Study (UKPDS) analysis, is has shown every 10 mm Hg reduction in systolic BP is related to the reduction factor of microvascular complications with a small risk among patients with systolic BP >120 mm Hg.[2]. Systolic and diastolic blood pressure was measured according to current guidelines. Age-specific normal values were obtained from the Task Force on Blood Pressure Control in Children and Adolescents. [49] The risk for cardiovascular events synergistically increases in patients with both diabetes mellitus and hypertension [1, 7, 2, 10]. The frequency of hypertension is elevated with the progression of renal damage in both diabetic and nondiabetic patients [7].

3. **Proteinuria:** This can advance to DN on its self. >2g/24 h of proteinuria shows a greater risk of EDRD. When the leakage of albumin is increased, it might probably include the glomerular damage but only through the activation of inflammatory cascades. It has been shown that the treatment of DN base on proteinuria is by decreasing urinary albumin secretion. [1, 2, 10] The prevalence of DN is high in patients with T2DM manifesting heavy proteinuria. Renal biopsy should be performed in diabetics in the atypical clinical scenario [42].

4. **Smoking:** It is another risk features of DN and can lead to advancement. Although some of the research did not confirm the observation. So it is advised that an individual should stop smoking in any of the stages of DN to avoid any kind of heart and cancer risk. [2] Inflammation is associated with increased resting energy expenditure (REE) in patients with chronic kidney disease. Oxidative stress, on the other hand, appears not to increase REE. Smoking is a common mechanism for generating oxidative stress and inflammation. Whether smokers have increased REE and if so, whether it is accounted for by the prooxidant and inflammatory state is not known [2, 6, 10].

5. Dyslipidemia: High serum cholesterol has been seen to be a great risk factor for GFR loss of macroalbuminuria in type 1 DM. An increase in the serum cholesterol level leads to the development of DN in type 2 DM while in type 1, an increase in patient serum triglycerides, total and LDL cholesterol are all related to macro and microalbuminuria. [1, 3, 10] HDL and LDL cholesterol were treated as independent, continuous variables, whereas for macroalbuminuria, dyslipidemia was treated as a dichotomous variable. [49]. Increasing evidence suggests that obesity is a risk factor for diabetes and chronic kidney diseases. As a marker of obesity, high body mass index (BMI) has been reported to be related to diabetic nephropathy (DN) and ESRD [8].
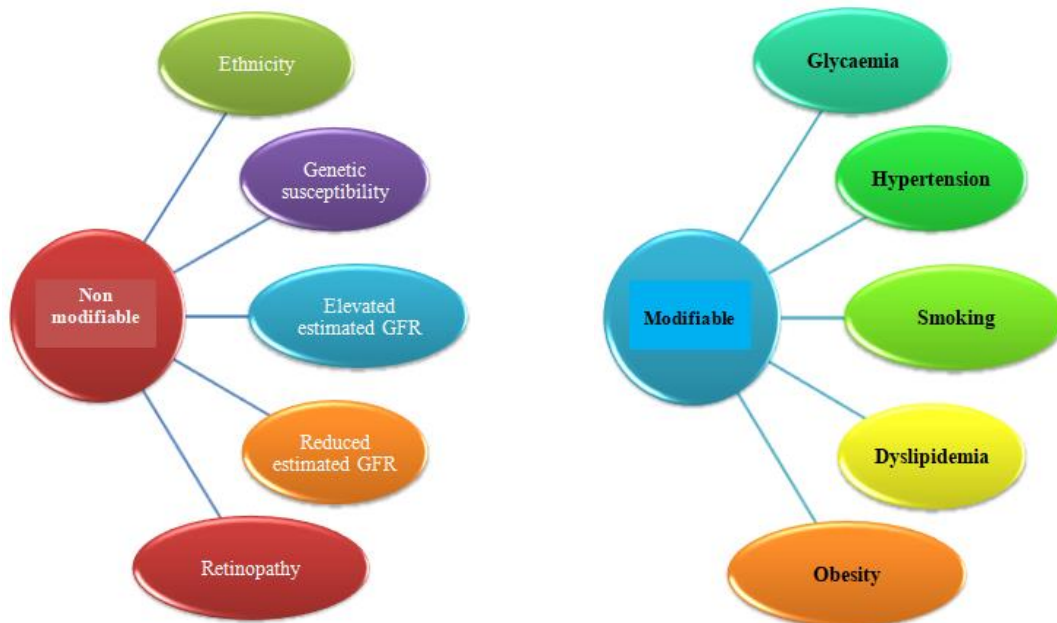

Figure 2: Risk factors that contribute to the development of DN [44]

6. Others: Oxalosis is a metabolic disorder characterized by the deposition of oxalate crystals in various organs including the kidney. Whereas primary forms result from genetic defects in oxalate metabolism, secondary forms of oxalosis can result from excessive intestinal oxalate absorption or increased endogenous production, e.g. after intoxication with ethylene glycol. Acute secondary oxalate nephropathy due to excessive dietary intake of oxalate may lead to acute renal failure in patients with a preexisting renal disease like mild diabetic nephropathy. Attention should be paid to special food behaviors when reasons for acute renal failure are explored. [46]

i. P2Y2R Deficiency

P2Y2R deficiency attenuates diabetic nephropathy [40]. Activation of purinergic receptors including P2Y2R has been associated with the pathogenesis of renal diseases such as polycystic kidney and glomerulonephritis. [52] However, the role of P2Y2R and its precise mechanisms in DN remain unknown. We hypothesized that P2Y2R deficiency may play a protective role in DN by modulating the autophagy signaling pathway. [50]. Hyperglycemia and Adenosine triphosphate (ATP) release were induced in wild type DN mice and positively correlated with renal dysfunction. [51] Conversely, P2Y2R knockout markedly attenuates albuminuria, podocytes loss, and the development of glomerulopathy, renal tubular injury, apoptosis, and interstitial fibrosis induced by DN.[53] These protective effects were associated with inhibition of Protein kinase B (AKT)-mediated Forkhead box protein (FOXO3a) phosphorylation and induction of FOXO3a-induced autophagy gene transcription.[59]Furthermore, inhibitory phosphorylation of ULK-1 was decreased, and the downstream Beclin-1 autophagy signaling was activated in P2Y2R deficiency. An increased SIRT-1 and FOXO3a expression in P2Y2R deficiency also enhanced autophagy response, thereby ameliorating renal dysfunction in DN. [58, 60]. P2Y2R contributes to the pathogenesis of DN by impairing autophagy and serves as a therapeutic target for treating DN. P2Y1R deficiency protected against renal capillary loss, fibrosis, and apoptosis in a crescentic glomerulonephritis model. [58] Subsequent analysis showed that the decrease of podocyte number is a good predictor of progression of albuminuria. [22]
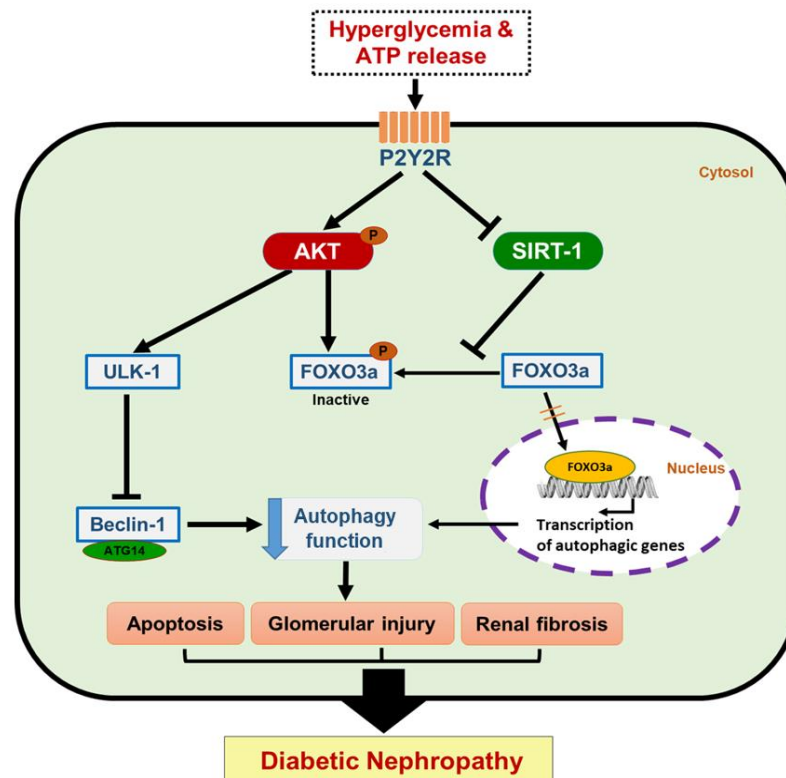
Fig 3 Schematic molecular mechanism of P2Y2R in the development of DN

P2Y2R activation via hyperglycemia and extracellular ATP increases AKT phosphorylation, and the increased AKT activity promotes inhibitory ULK-1 phosphorylation that down-regulates autophagy through inhibition of Beclin-1 and ATG14 complex required for phagophore formation, resulting in renal apoptosis, glomerular injury, and interstitial fibrosis. Also, the increased phosphorylation of FOXO3a by AKT activity and the inhibited SIRT-1(Selective Internal Radiation Therapy) activity reduced autophagy response by downregulating transcription of autophagy genes. Conversely, P2Y2R knockout mice have reduced AKT phosphorylation and increased FOXO3a and SIRT-1 expression to rescue autophagy response and attenuate the progression of DN. [40, 54 – 57].

ii. Diets

The candidate anti-diabetic drug, [RuII(H3ucp)Cl(PPh3)](H4ucp=2,6-bis-((6-amino-1,3- dimethyl-uracil imino)methylene)pyridine exhibited Renoprotective effects in HFHC diet-induced pre-diabetic rats by reducing blood glucose, fluid intake, and urinary output while ameliorating oxidative stress and antioxidant defense enzymes, reducing aldosterone and KIM-1 concentrations.[37].

iii. Epithelial-to-mesenchymal transition (EMT)

An evolutionarily conserved biologic process that epithelial cells were transdifferentiated into motile mesenchymal cells, is involved with the wound healing and stem cell behavior, and the progression of fibrosis and cancer. In the process of EMT, their epithelial characteristics are disappeared, including the loss of cell-cell junctions and apical-basal polarity, cytoskeleton reorganization, and are with high production of extracellular matrix (ECM), indicating the promoted migratory and invasive ability [72, 73] Additionally, it is widely recognized that EMT is a key process that contributes to DN, resulting to tubulointerstitial fibrosis, and even ESRD. It was uncovered that epithelial cells were in the process of EMT in kidney fibrosis tissues [74], and the increased serum creatinine level and the severity of interstitial damage are associated with the number of mesenchymal marker-positive epithelial cells [75,76]. Furthermore, mesenchymal-like α-smooth muscle actin (α-SMA)-positive epithelial cells were identified in the kidney tissues from DN patients, indicating that epithelial cells are undergoing EMT in the kidney in DN.

D. Pathophysiology and pathogenesis of DN

1. Age/ Rage/Nox signaling-mediated ER stress

After exposure to pathologic stimuli (e.g., high glucose, advanced glycation end-products (AGEs), and Reactive oxygen species. (ROS), the renal cells are triggered by several signaling cascades that facilitate chronic inflammation. AGEs interact with Receptor for AGEs (RAGE) and activates NADPH oxidase (Nox2) at Endoplasmic reticulum (ER) and cell membranes, as well as, Nox4 at the ER membrane. Apart from AGEs, High mobility group box (HMGB1) and S100/calgranulins are other ligands for RAGE. Protein kinase C (PKC) is also upstream of Nox. To exert a pro-inflammatory effect, Nox induces ROS production and Inhibitory kappa B kinase (IKK)-dependent Jun N-terminal kinase (NF-κB) activation. Meanwhile, Nox activation leads to ER stress. In response to ER stress, UPR proteins, which are composed of PKR-like eukaryotic initiation factor 2α kinase (PERK), activating transcription factor (ATF) 6, and Inositol requiring enzyme (IRE1) enhance the adaptive pathway to maintain ER proteostasis via ATF4, ATF6, and X-box binding protein (XBP1), respectively. In prolonged ER stress, ATF4 induces CHOP (enhancer-binding protein homologous protein) to discard dysfunctional proteins in the apoptotic pathway. UPR transducers interfere with lipogenesis and gluconeogenesis genes. ER stress alters insulin signaling and causes insulin resistance by IRE1/JNK (Jun N-terminal kinase) signaling and JNK-dependent IRS-1(Insulin receptor substrate) serine phosphorylation. Also, IRS-1 can be downregulated by PKC (Protein kinase C). In the end, AGE/RAGE/Nox signaling-mediated ER stress causes kidney inflammation, glomerular hypertrophy, podocytes injury, proteinuria, and eventually renal fibrosis. [3]. AGE/RAGE/Nox signaling triggers ER stress in DN. Targeting at critical molecules of this axis, including RAGE, Nox, and UPR-transduced proteins (i.e., PERK, ATF6, and IRE1), will be beneficial in treating these diseases and other relevant kidney disorders. Specific miRNAs and lncRNAs can rescue those pathological events by interfering at particular targets, highlighting ncRNAs as a new layer of therapeutic strategies against DN. We prospect that ncRNAs listed in this review, with the exosomal delivery system, will pave the way for the ncRNA-based therapeutic approach in kidney diseases related to AGE/ RAGE/Nox/ER stress cascade. [3]

2. Inflammatory pathways, oxidative stress, and epigenetic factors

Pathogenesis of DN is a complex and multifactorial process that appears to be a combination of inflammation, oxidative stress, and epigenetic factors [79, 80]. However, the role of glomerular hyperfiltration early in the course of diabetes lies at the heart of the pathophysiology of DN. Vallon et al., established this through the single-nephron GFR studies, which showed that the dysregulated tubuloglomerular feedback (TGF) in diabetic rats leads to a reduced tone in afferent arteriole which causes glomerular hypertension [81]. Hence, it is important to understand that

a) juxtaglomerular apparatus fine-tunes the glomerular filtration and is an important homeostatic mechanism that regulates glomerular pressures

b) adenosine is an important mediator of TGF; and

c) in diabetes, the activity of sodium-glucose transporter (SGLT-2) is increased, leading to enhanced absorption of sodium in the proximal convoluted tubule.

This results in a decreased distal delivery of sodium, which in turn signals the TGF mechanism to decrease the afferent arteriolar tone. Ultimately, this leads to glomerular hyperfiltration, thus begins the pathologic changes of DN [20]. The mechanism of decreased distal sodium delivery leading to glomerular hyperfiltration was confirmed by the phenomenon called the "salt paradox". In this phenomenon, when rats in early phases of diabetes were salt-restricted, they absorbed most of the sodium in the proximal convoluted tubule that lowered the delivery of sodium to the distal convoluted tubule. This decreased local adenosine levels resulting in the dilation of the afferent arteriole. We refer readers to Vallon et al. for an excellent review of these mechanisms [81]

E. Management of diabetic nephropathy

Many of the therapeutic modalities are already approved by clinical trials that proved the safety and efficacy of these modalities. Others are still waiting for this approval. These 2 categories will be discussed under ''Approved treatment'' and ''Potential therapeutic modalities'' respectively [5]. A multidisciplinary approach for management [44] for DN is recent approach. DN and ESKD remain a significant clinical problem. In diabetic individuals in whom no single treatment can halt the progression of DN, a multidisciplinary approach delivered by a multi-professional team remains the most sensible strategy. The main goals are Reno-protection and optimization of treatment using ACE inhibitors or ARBs increasing to the maximum dose, restrict salt intake with a diuretic, RAS blockers, and calcium-channel blocker. In

addition to this, statins according to requirement, fibrates to lower cholesterol. Apart from this, all the risk factors should be taken care of. There are several methods of treating DN, which include the use of Drugs (table.2.), enzymes/Antibodies, Nano formulations, etc.

Vascular endothelial growth factor B (VEGF-B) is a crucial factor in promoting abnormal lipid metabolism as a part of the vascular endothelial growth factor family[61]VEGF-B can specifically up regulate fatty acid transport proteins (FATPs) and increase ectopic lipid deposition, which ultimately leads to insulin resistance by binding to the membrane receptors neuropilin-1 (NRP-1) or vascular endothelial growth factor receptor (VEGFR)-1[62]. Recent studies have reported that VEGF-B can also promote lipid accumulation in podocytes and directly result in DN by reducing podocytes' insulin sensitivity[33]. Therefore, an anti-VEGF-B monoclonal antibody is expected to treat DN by simultaneously regulating lipid metabolism and improving insulin resistance. However, there is no definitive evidence that reducing VEGF-B signaling could alleviate oxidative stress and inflammatory responses, which are equally the leading causes of DN [63 - 65] Antagonism of VEGF-B could efficiently ameliorate DN by reducing renal lipotoxicity [39]. IL-22 (Interleukin) can be produced by CD4 T (cluster of differentiation 4) helper subtypes (such as Th17 cells and Th22 cells) and innate lymphoid cells (ILCs, such as natural killer cells, dendritic cells, and macrophages) as one of the interleukins-10 cytokine superfamilies'[66] IL-22 mainly binds to the receptors IL-22R1 and IL-10R2, and then specifically activates the intracellular JAK/STAT3(Janus kinase/signal transducers and activators of transcription) signaling pathway, thereby mediating anti-inflammatory and other biological effects [67 - 69]. IL-22 can significantly reduce inflammatory cytokines (such as IL-1b) and simultaneously protect renal function in DN mice.[70] Moreover, studies have also indicated that IL-22 can alleviate renal injury caused by renal ischemia-reperfusion.[71] Thus, we hypothesize that combining VEGF-B antibody and IL-22 can alleviate renal lipotoxicity and insulin resistance as well as ameliorate inflammatory responses.[33]

Table 2. Drugs for the treatment of DN

Drug Name	Uses	Side Effects	Reference
Lisinopril	ACE Inhibitors	Dizziness, hypotension, hyperkalemia, increased blood urea nitrogen	2,89
Enalapril		Dizziness	
Trandolapril		Fever, sweating	
Ramipril		Dizziness,	
Quinapril		Fever, sweating	
Canagliflozin	SGLT-2 inhibitor	loss of appetite	20
Perindopril	ACE Inhibitors	Dizziness, sweating	2,89
Moexipril		Fever, sweating	
Benazepril		Dizziness,	
Losartan	AR Blockers	Fever, sweating Dizziness	
Irbesartan		Fever, sweating Dizziness	
Fosinopril	ACE Inhibitors	Dizziness,	
Captopril		Fever, sweating	
Quinapril		Fever, sweating	
Pyridoxamine		nausea, vomiting, diarrhea	90,2
R-147176		Nausea, Vomiting	
Benfotiamine		Upset stomach. Nausea. Dizziness.	
Alagebrium (ALT-711)		None	90,2
Kremezin (AST-120)	Retards progression of CKD	Appetite loss, Nausea, and Vomiting	
Pentoxifylline	Prevents the enhanced expression of cytokine and IL	Nausea, vomiting, gas, belching	
Ruboxistaurin	Reduces the actions of VEGF	Dyspepsia.	
Aliskiren	AR Blockers	Nausea, Vomiting, Diarrhea.	
Sulodexide	Decreasing the concentration of glycosaminoglycans	Dyspepsia,Heartburn,Dizziness	
Naproxen	Anti-inflammatory Drug	Nausea and Vomiting.	6,90
Ibuprofen			
Diclofenac			
Aspirin			

b .Recent approach in management using nano-formulations

Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specifically targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of precise medicines. Recently, there are several outstanding applications of nanomedicine (chemotherapeutic agents, biological agents, immunotherapeutic agents, etc.) in the treatment of various diseases. [84] Nanotechnology is the measurement and manipulation of material at the level of 1– 100 nanometres (nm), 1 nm being 10−9 or one billionth of a meter (Nanos, Greek, 'dwarf'). When this science is applied specifically to the problems of medicine, it is called 'nanomedicine' [85] The current review, presents an updated summary of recent advances in the field of nanomedicines and nano based drug delivery systems through comprehensive scrutiny of the discovery and application of nanomaterials in improving both the efficacy of novel and old drugs (e.g., natural products) and selective diagnosis through disease marker molecules. The opportunities and challenges of nanomedicines in drug delivery from synthetic/natural sources to their clinical applications are also discussed. In addition, we have included information regarding the trends and perspectives in Nanomedicine area. [84]

Nanoparticles used in drug delivery system

Numerous biopolymeric materials are utilized in drug delivery systems. These materials are:

1. Chitosan is a linear polysaccharide composed of randomly distributed β-(1→4)-linked D-glucosamine (deacetylated unit) and *N*-acetyl-D-glucosamine (acetylated unit). It is made by treating the chitin shells of shrimp and other crustaceans with an alkaline substance, such as sodium hydroxide.

2. *Alginate is a*nother biopolymeric material that has been used as drug delivery is alginate. This biopolymer presents final carboxyl groups, being classified as anionic mucoadhesive polymer, and presents greater mucoadhesive strength when compared with cationic and neutral polymers **[**91, 92**].**

3. *Xanthan gum* (XG) is a high molecular weight heteropolysaccharide produced by *Xanthomonas campestris*. It is a polyanionic polysaccharide and has good bioadhesive properties. Because it is considered non-toxic and non-irritating, xanthan gum is widely used as a pharmaceutical excipient [93].

4. *Cellulose* and its derivatives are extensively utilized in the drug delivery systems basically for modification of the solubility and gelation of the drugs that resulted in the control of the release profile of the same [94].

5. *Liposomes* They were discovered by Alec Bangham in 1960. Liposomes are used in the pharmaceutical and cosmetics industry for the transportation of diverse molecules and are among the most studied carrier system for drug delivery. Liposomes are an engrained formulation strategy to improve drug delivery. They are vesicles of spherical form composed of phospholipids and steroids usually in the 50–450 nm size range [95].

6. *Polymeric micelles* are nanostructures made of amphiphilic block copolymers that gather by themselves to form a core-shell structure in the aqueous solution. The hydrophobic core can be loaded with hydrophobic drugs (e.g. camptothecin, docetaxel, paclitaxel), at the same time the hydrophilic shell makes the whole system soluble in water and stabilizes the core. Polymeric micelles are under 100 nm in size and normally have a narrow distribution to avoid fast renal excretion, thus permitting their accumulation in tumor tissues through the EPR effect. [96]

7. *Dendrimers* are highly bifurcated monodisperse, well-defined, and three-dimensional structures. They are globular-shaped and their surface is functionalized easily in a controlled way, which makes these structures excellent candidates as drug delivery agents[102-104].

8. *Inorganic nanoparticles* include silver, gold, iron oxide, and silica nanoparticles are included. Studies focused on them are not as many as there are on other nanoparticle types discussed in this section although they show some potential applications.

9. *Nanocrystals* are pure solid drug particles within the 1000 nm range. These are 100% drugs without any carrier molecule attached to them and are usually stabilized by using polymeric steric stabilizers or surfactants.

10. *Metallic nanoparticles* in recent years, the interest in using metallic nanoparticles has been growing in different medical applications, such as bioimaging, biosensors, target/ sustained drug delivery, hyperthermia, and photoablation therapy [101, 100].

Examples of Nano formulations

1. Insulin as nanoparticle

To mimic native insulin activity, materials have been developed that encapsulate insulin, glucose oxidase, and catalase for glucose-responsive insulin delivery. A major challenge, however, has been achieving the desired kinetics of both rapid and extended-release. Here, we tune insulin release profiles from polymeric nanoparticles by altering the degree of modification of acid-degradable, acetylated-dextran polymers. Nanoparticles synthesized from dextran with a high acyclic acetal content (94% of residues) show rapid release kinetics, while nanoparticles from dextran with a high cyclic acetal content (71% of residues) release insulin more slowly. [82]

2. Ursodeoxycholic acid As Nano formulation

Ursodeoxycholic acid (UDCA) is a secondary hydrophilic bile acid, metabolized in the gut, by microbiota. UDCA is currently prescribed for primary biliary cirrhosis and recently has shown βcell-protective effects, which suggests potential antidiabetic effects. Thus, this study aimed to design targeted delivery microcapsules for oral uptake of UDCA and test its effects in type 1 diabetes (T1D). UDCA microcapsules brought about a reduction in elevated blood glucose, reduced inflammation, and altered concentrations of the primary bile acid chenodeoxycholic acid, and the secondary bile acid lithocholic acid, without affecting the survival rate of mice. [86]

3. Oral administration of angiotensin-(1–7) ameliorates type 2 diabetes

It has been shown that activation of the angiotensin (Ang)-(1–7)/Mas axis of the renin-angiotensin system leads to improved glucose uptake. In the recent study, it was intended to evaluate, whether this effect could be exploited therapeutically. It was first confirmed that Ang-(1–7) improves insulin signaling and glucose uptake in vitro in cultured cardiomyocytes. An oral Ang-(1–7) formulation reverses hyperglycemia and its consequences in an animal model of DM2 and represents a novel therapeutic option for the treatment of DM2 and other cardio-metabolic diseases [1]

4. Metformin

Metformin HCl belongs to class biguanides. It is considered the first-line agent for the treatment of patients newly diagnosed with type 2 diabetes as a supplement to diet and exercise, despite its drawbacks of short biological half-life of 1.5–1.6 h and daily requirement of 1.5– 3 g/day with an absolute bioavailability of 50–60% when administered orally. Metformin HCl niosomal gel (applied transdermally every 2 days) has a better sustained anti-diabetic effect as compared to the orally given metformin HCl tablets (given daily) which also helped to alleviate the problems associated with oral metformin HCl tablets. Also, one of the main results achieved from this is the capability of using metformin HCl niosomal patches for helping the enhancement and improvement of wound healing that represent a vital problem for diabetic patients. Hence, the optimized transdermally applied niosomal formulations represent a promising carrier for metformin HCl to provide a better lifestyle for diabetic patients. [87] The combined synergistic effects of Metformin and biopolymers are due to their corresponding mechanism to enhance glucose uptake, minimized the adverse effects during diabetic therapy[88].

II. CONCLUSION

DN is a global concern and its treatment is required to consider from the time of initiation of diabetes. Patients must consider all the restrictions of diet and they must take the drug on time. It is also very important that they must be aware of all the complications associated with it. The advancement of technology used in drug formulations and its development indicates that scientists are working very hard to treat this. These nanoformulation aspects are very successful to control diabetes.

Conflict of interests

None

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