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Emerging Complications and Risks of Diabetes Mellitus: An Emphasis on Diabetic Nephropathy

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Abstract: Diabetic nephropathy is a common complication of Type I and Type II diabetes. Over time, poorly controlled diabetes can cause damage to blood vessel clusters in kidneys that filter waste from the blood. The development and progression of Diabetic Nephropathy (DN) is complicated, multifaceted, involving numerous routes and mediators. The diabetic nephropathy development is typically by aberrant equilibrium, which includes issues with homeostasis, metabolic issues, and issues with hormone synthesis like Angiotensinogen –II. Different symptoms can be seen such as increase in blood pressure, urine containing protein, swelling in the hands, eyes, ankles, and feet, and increased urine urgency, breathing difficulty, appetite loss, confusion or trouble paying attention, sickness, vomiting, constant itching, fatigue, etc. In this review, detailed description on *in vitro* and *in vivo* animal models used in screening of diabetes and its complication is given. Plant based research is gaining significance in the present era. The different plants used in the treatment were highlighted and pathogenesis, diagnosis and treatment are explained in a detail.

Keywords: Diabetes, Nephropathy, Type I DM, Type II DM, Kidney

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Introduction

Diabetes patients who have certain kidney problems in both structural and functional ways are said to have diabetic nephropathy (DN). The structural changes include increase in glomerulus membrane thickness, kidney enlargement and nodule formation. The

functional changes are initial rise in GFR associated with Intraglomerular Hypertension, followed by excretion of proteins through urine, increased blood pressure, and eventually results in decreased function of kidney (Fineberg *et al.*, 2013). Type I diabetes patients

play the main role which helps in understanding the history of diabetic nephropathy. But people with type II diabetes exhibit identical histology symptoms. Diabetes related kidney disease has been extensively studied in terms of both its clinical signs and histological effects. The pathophysiology of diabetes is not well known, even though there are numerous causative reasons that are linked to its diseased conditions, as longitudinal data and kidney biopsies are lacking. Here, we will concentrate on the pathogenesis while assessing what is currently known about the histology and clinical correlations and highlighting any unanswered issues (Tavafi, 2013).

Pathogenesis:

The development and progression of Diabetic Nephropathy is complicated, multifaceted, involving numerous routes and mediators. The diabetic nephropathy development is typically by aberrant equilibrium, which includes issues with homeostasis, metabolic issues, and issues with hormone synthesis like Ang-II (Kopel *et al.*, 2019). The renin angiotensin aldosterone system, the production of glycation end products such as, reactive oxygen species, transforming growth factor-1, connective tissue growth factor, protein kinase C, and mitogen-activated protein kinases are critical pathways for the development of DN. Every pathway engages in interactions with other pathways or causes cellular harm through a number of mediators. The pathways and mediators are very overlapping; for instance, Ang-II damages cells via oxidative stress, whereas oxidative stress damages cells via RAAS. Nicotinamide adenine phosphate dehydrogenase oxidase is activated by NADPH oxidase, and ROS is activated by TGF- β . As a result, it is unclear how much each pathway contributes to DN induction (Agarwal, 2021).

The four causal elements that initiate and sustain the pathogenesis of diabetic nephropathy are metabolic, hemodynamic,

growth and pro-inflammatory. We shall analyse the pathophysiology as if each piece had an independent role, despite the fact that these components frequently overlap one another and that there is fluctuation in their contributions over the time and among the individuals. The glomeruli, tubuli, interstitium, and vasculature are only a few of the renal compartments where these pathogenic agents might cause diseases. From the earliest stages of kidney disease, including hypertrophy, glomerulo sclerosis, interstitial fibrosis, expanded extracellular matrix, tubular atrophy, and functional loss, vascular hyalinosis, to end-stage renal disease, a complex network of molecules, receptors, enzymes, and transcription factors are involved.

Symptoms:

Symptoms of diabetes are -- Increased blood pressure, urine containing protein, swelling in the hands, eyes, ankles, and feet, and increased urinal need, decreased requirement for insulin or diabetes medication, confusion or trouble paying attention, breathing difficulty, appetite loss, sickness, vomiting, constant itching, and fatigue.

Screening Tests:

The following are the common screening tests that are used for diabetic nephropathy diagnosis:

Urine Albumin Test:

Urine is tested for albumin, a blood protein. Generally, Albumin is not eliminated by the kidneys. Unhealthy kidney function may be indicated by excessive protein in the urine.

Albumin/Creatinine Ratio:

In good kidney health, the kidneys remove creatinine from the blood as a chemical waste product. The albumin/creatinine ratio (Table 1), which gauges how much albumin and creatinine are present in a urine sample, is another indicator of kidney health.

Table 1: Albumin/creatinine ratio in urine

SCREEN	NORMAL	MODERATE	SEVERE
Excretion rate of Albumin (mg/24 h)	Less than 30	30 to 300	More than 300
Albumin creatinine ratio (mg/g)	Less than 30	30 to 300	More than 300
Albumin creatinine ratio (mg/mmol)	Less than 3	3 to 30	More than 30

Table 2: Microscopic examination for diabetes nephropathy

Disease	Clinical Manifestations	Light Microscopy	Immunofluorescence Microscopy	Electron Microscopy
DN	Chronic diabetic condition	Nodular sclerosis; PAS (+) Silver (+)	(Ig)G Immunoglobulin deposition takes place linearly, with or without C3 and IgM in the nodules.	Expansion of mesangial tissue; Glomerular base membrane thickening; fibrillar deposition which is non-specific.

GFR:

The level of Creatinine in the blood sample is used to determine the glomerular filtration rate of the kidneys. Kidney's function will be weak when the filtration rate is low.

Kidney Image Test:

Ultrasound and X-ray technology are used to assess the size and structure of kidneys. CT or MRI scan can also be performed to determine how well the blood is passing through kidneys.

Kidney Biopsy:

Kidney biopsy may be performed in which a few tiny pieces of kidney tissue are taken with a fine needle for microscopic examination (Table 2).

Clinical Features:

Initially in the first 10 years, T1DM patients will slightly develop DN symptoms; however,

between ten and twenty years, the incidence of DN is about three per cent per year. An additional 15% of T1DM patients have severe albuminuria, whereas 15% have moderate albuminuria. In those with normal renal function and normal urine albumin excretion after 30 years of getting T1DM, the incidence rate drops after 20 years, reducing the risk of developing DN (Selby and Taal, 2020). As a result, the likelihood of getting DN differs between people and depends on a number of other variables as well, including glycemic management, blood pressure, and genetic vulnerability.

Histological Features:

A limited number of DN patients require kidney biopsy for the diagnosis; the main descriptive findings have been specified in an International categorization system. From Classes 1 to 4 are distinguished by severe glomerulosclerosis, mesangial enlargement,

Table 3: Drugs used in type I and II DM

Drugs	Antiproteinuric	Preserve GFR	Diabetes Type
ACE	+ve	+ve	Type I and II
ARB	+ve	+ve	Type II
ACE + ARB inhibitors	+ve	-ve	Type I and II
Aldosterone antagonist	+ve	-	Type II
Aldosterone antagonist + ACE blocker or ARB	+ve	-	Type I and II
Renin inhibitor	+ve	-	Type II
Renin inhibitor + ACE blocker or ARB	+ve	-	Type II
Non- dihydropyridine CCB	+ve	-	Type II
Non- dihydropyridine CCB with ACE inhibitor or ARB	+ve	-	Type II
Statin	+ve	-	Type II
Vit D	+ve	-	Type II

ACE = Angiotensin converting enzyme; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; GFR = Glomerular filtration rate (Lim, 2014)

nodular sclerosis, and thickening of basement membrane of glomerulus respectively. Along with these different features of glomerulus, interstitial-fibrosis, interstitial tubular atrophy, arteriolar-hyalinosis, and arterio-sclerosis are frequently observed (Tervaert *et al.*, 2010).

Factors at Risk:

All the diabetics patients would not develop diabetic nephropathy, and when it develops, the course is uncertain. The primary preventable risks include hypertension, glycemic control, and dyslipidemia. Smoking is the main factor of risk for developing diabetic nephropathy (Tapp *et al.*, 2004). Age, race, and genetic makeup are the primary unchangeable risks. Patients who have DN in their families are more likely to develop the condition. According to one study, men may be more susceptible to DN (Gall MA *et al.*, 1997).

Treatment:

The four main therapeutic foci for individuals with diabetic nephropathy are glycemic management, blood pressure control, RAS inhibition, and cardiovascular risk reduction. Table 3 illustrates the drugs which can be used for improving kidney function in Type I and II DM.

Screening Models for Diabetic Nephropathy:

Table 4 depicts various screening models for DN.

(1) Models for Type I DM:

(i) STZ induced mice model:

Because streptozotocin is harmful to beta cells of pancreas and this will result in a greater lack of insulin, it is a common model to induce experimental type I DM in mice. Streptozotocin may be hazardous for other organs, including the kidney, in addition to pancreatic beta cells (Wilson and Leiter, 1990).

Table 4: Screening models for DN

Types	Sub-types
1. Rat models for type I diabetes.	• <i>STZ induced Type-I diabetes mice model.</i> • <i>C57BL/6 rat model.</i>
2. Genetic Type II diabetes mice models.	• <i>Akita Ins2+ / C96Y mutant Mice model.</i> • <i>OVE26 FVB Mice model.</i>
3. Rodent Type II diabetic models.	a) Mouse models • db by db mice model. • KK and KK-Ay mice model. • High-fat diet-induced type-II diabetic mice model.
	b) Rat models • Diabetic fatty rat model (Zucker). • ZDF rat model. • WF Rat model. • Fatty rat model (Otsuka Long-Evans Tokushima). • <i>GK Rat model.</i> • <i>T2DN/Mewi rat model.</i>

(i) *Akita Ins2+ / C96Y model:*

Therefore, STZ dosages of 150–200 mg/kg should not be administered to mice. The AMDCC protocol recommends this method, which entails with regular IP injections with dose of 40 to 50 mg per kg of streptozotocin for a total of five days (Bolzán and Bianchi, 2002).

(ii) *C57BL/6 Model:*

The most popular strain of mouse in preclinical research is the C57BL/6 mouse, which has undergone numerous genetic alterations due to its high reproductive efficiency, long lifespan, and low susceptibility to cancer. This strain is not particularly vulnerable for initial renal injury in experimental models for diabetic DN (Breyer *et al.*, 2005).

(2) *Genetic Models:*

These types of mice have the Ins2+ /C96Y mutation, a single nucleotide alteration in the Ins 2 genome. Type I diabetes is brought on by the Ins2+/C96Y mutation, which impairs the pancreatic beta cells ability to release insulin and causes incorrect folding of protein (insulin) (Alpers and Hudkins, 2011). The C57BL/6 Akita diabetic mice first displayed modest albumin content in urine and mild abnormalities in the structural way, including in the rise of mesangial matrix, thickening basement membrane of glomerulus, podocytes depletion, these are partly triggered by an increase in apoptosis. Numerous studies on the renal system of these mice have also been conducted, and these have demonstrated inflammation and oxidative stress. The development of diabetic nephropathy depends

on these circumstances (Susztak *et al.*, 2006).

(ii) OVE26 FVB mice model:

Calmodulin is transgenically overexpressed in pancreatic cells in OVE26 mice, which causes type I diabetes to manifest within the first week of life due to insufficient insulin production. Inflammation and oxidative stress brought on by diabetes are linked to diabetic nephropathy in OVE26 mouse kidneys. The main characteristics of these mice are human diabetic nephropathy and persistent hyperglycemia. As a result, this model may further be used for understanding the pathophysiology of DM and may lead to the development of treatments for DN (Xu *et al.*, 2010).

(3) Rodent Models of Type II Diabetes:

(a) Mouse models:

(i) db by db model for mice:

Based on these mice, this type II diabetes model is the most widely used. Their leptin receptor (LepRdb/db) has a deletion mutation which leads to incorrect splicing and a defective receptor for adipocyte production which produces the leptin hormone. By altered hypothalamic responses as a result of the LepRdb/db deletion's impact on leptin signalling hyperlipidemia, hyperinsulinemia, insulin resistance, obesity, hyperphagia and diabetes can be produced (Tesch and Lim, 2011). Diabetes affects male mice more severely than female mice.

(ii) KK and KK-Ay model for mice:

This strain (KK) which Kondo *et al.* (1957) created by inbreeding a Japanese mouse, has modest obesity and insulin resistance, these are more in male than in females. Albuminuria in KK mice seems to emerge about 10–15 weeks of age, although its reasons are yet unknown. The increased albuminuria seen in STZ induced diabetic KK /H1J mice demonstrates susceptibility to albuminuria in a diabetic condition (Tomino *et al.*, 2005).

(iii) High fatty diet mice model:

A high fatty diet will promote systemic alterations in the metabolic system of rats, these include insulin resistance, hyperglycemia, obesity and abnormal lipid profiles (Deji *et al.*, 2009). The alterations will closely mimic the metabolic syndrome, which is linked to type II diabetes.

(b) Rat Models:

(i) Zucker Wistar fatty rat model:

The ZF rats will develop obesity but not diabetes due to a homozygous mis-sense mutation in the leptin receptor gene. Research on type II diabetes typically uses the Zucker diabetic fatty, a strain of rats descended from the Zucker fatty (ZF) strain that exhibits diabetes and obesity (Phillips *et al.*, 1996).

(ii) ZDF rat model:

ZDF rats begin to exhibit evidence of escalating insulin resistance and glucose intolerance between the ages of 3 and 8 weeks, and between the ages of 8 and 10 weeks, they are unmistakably diabetic. At 6 weeks of age, male ZDF rats have somewhat greater levels of albuminuria than control lean rats (Vora *et al.*, 1996). Following that, albuminuria in the rats gradually rises with the age by 36 weeks of age.

(iii) WF rat model:

Similar to the ZFD rats, these rats will develop obesity, intolerance to glucose, and increasing levels of insulin resistance between the ages of 3 and 8 weeks. Between the ages of 8 and 10 weeks, they show overt signs of diabetes. In contrast to WF rats and ZFD rats have a mild level of diabetes (Kitada *et al.*, 2016).

(iv) Fatty rat model (Otsuka Long-Evans Tokushima):

These rats are well-known type II DM models. Male rats (OLETF) begin to exhibit impaired glucose tolerance at the age of 8 weeks and by 18 weeks the levels of plasma glucose will increase. Due to peripheral insulin resistance

Table 5: Some of the plants used for anti-diabetic action

S. No.	Botanical Name	Family Name	Common Name	S. No.	Botanical Name	Family Name	Common Name
1	<i>Allium sativum</i>	Amaryllidaceae	Garlic	18	<i>Psidium guajava</i>	Myrtaceae	Guava
2	<i>Anacardium occidentale</i>	Anacardiaceae	Cashew	19	<i>Phyllanthus emblica</i>	Grossulariaceae	Gooseberry
3	<i>Andrographis paniculata</i>	Acanthaceae	Kalmegh	20	<i>Piper nigrum</i>	Piperaceae	Pepper
4	<i>Astragalus propinquus</i>	Fabaceae	Milk Vetch	21	<i>Pterocarpus santalinus</i>	Fabaceae	Red sandalwood
5	<i>Benincasa cerifera</i>	Cucurbitaceae	Kushmanda	22	<i>Panax quinquefolius</i>	Araliaceae	American Ginseng
6	<i>Brassica oleracea</i>	Brassicaceae	Red Cabbage	23	<i>Polygonatum odoratum</i>	Asparagaceae	Scented Solomon's Seal
7	<i>Cinnamomum cassia</i>	Lauraceae	Cinnamon	24	<i>Rheum officinale</i>	Polygonaceae	Rhubarb
8	<i>Curcuma longa</i>	Zingiberaceae	Turmeric	25	<i>Syzygium aromaticum</i>	Myrtaceae	Clove
9	<i>Camellia sinensis</i>	Theaceae	Green tea	26	<i>Salvia miltiorrhiza</i>	Lamiaceae	Red Sage
10	<i>Coriandrum sativum</i>	Apiaceae	Coriander	27	<i>Silybum adans</i>	Asteraceae	Milk Thistle
11	<i>Cinnamomum zeylanicum</i>	Lauraceae	Dalchini	28	<i>Trigonella foenumgraecum</i>	Myrtaceae	Fenugreek
12	<i>Ganoderma lucidum</i>	Ganodermataceae	Lingzhi Mushroom	29	<i>Tectona grandis</i>	Lamiaceae	Teak Wood
13	<i>Gymnema montanum</i>	Asclepiadaceae	Bidaria Tingens Deche	30	<i>Terminalia chebula</i>	Combretaceae	Black Myrobalans
14	<i>Ginkgo biloba</i>	Ginkgoaceae	Maidenhair Tree	31	<i>Vitis vinifera</i>	Vitaceae	Grape Vine
15	<i>Glycine max</i>	Fabaceae	Soyabean	32	<i>Zingiber officinale</i>	Zingiberaceae	Ginger
16	<i>Indigofera tinctoria</i> Leaves	Fabaceae	True Indigo	33	<i>Linum usitatissimum</i>	Linaceae	Common Flax or Linseed
17	<i>Ocimum sanctum</i>	Labiatae	Tulasi		--	--	--

and islet cell hyperplasia, the disease's early stages are marked by hyperglycemia and hyperinsulinemia. Nearly all male rats will have DM by the age of 25 weeks (Nagai and Ito, 2013).

(v) GK rat model:

This model is a Type II DM model that is not fat. By selectively breeding rats with severe

blood glucose levels over several generations. These strains are developed from the Wistar rat colony. By the age of 2 weeks, GK rats show signs of glucose intolerance, and by the age of 4 weeks, they show severe blood glucose levels following with injection of a glucose load. This is brought about by both insulin resistance and the inadequate islet cell development, they produce insulin over

glucose. Type II diabetes, which is characterised by persistent increases in plasma glucose and fasting glucose, is present in GK rats by the age of 12 weeks (Östenson *et al.*, 1993). Experiments revealed that these rats have some resistance to DN development.

(vi) T2DN/Mewi rat model:

Nobrega *et al.* (2004) reported the emergence of a genetic alteration of sub-strain of GK from a cross between GK and Fawn-Hooded Hypertensive rats. By the age of six months, the T2DN/Mcwi rats have progressive proteinuria and hyperglycemia, along with histological changes in the kidneys, including severe mesangial matrix enlargement, glomerular basement membranes thickening, and localised glomerulosclerosis (Nobrega *et al.*, 2004). By the time the rats are 18 months old, nearly all of the Type-II DM rats have diffuse glomerulosclerosis with arteriolar hyalinosis and nodule formations.

Plant Based Research:

Hyperglycemia has a substantial impact on how diabetic nephropathy develops and advances. Due to their therapeutic qualities and lack of significant side effects, plants are the source of many modern medications. A few of the chemical compounds in plants that are used to treat diabetic nephropathy include alkaloids, glycosides, terpenoids and flavonoids (Shahin *et al.*, 2022).

As herbal treatments have become increasingly significant in recent years, the use of natural products in the treatment of diabetes has increased in popularity globally. More than 400 plant species have anti-diabetic action (Table 5) (Shafi *et al.*, 2012).

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