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OPTIMAL ANIMAL MODELS FOR DIABETIC NEPHROPATHY: BRIDGING THE GAP FROM BIOLOGY TO MEDICINE

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Abstract: Diabetes mellitus is a chronic condition characterised by elevated blood sugar level due to insufficient insulin production or inadequate insulin action. Diabetes nephropathy (DN) is one of the most significant side effects of Type 2 diabetes (T2D), caused by an excess of oxygen radicals. It is characterized by elevated blood sugar, glucose auto-oxidation, glycation of proteins, and the polyol activation mechanism and is characterized by the amount of albumin in the urine and a predicted glomerular filtration rate. Animal models can be used to investigate the pathophysiology of diseases and test potential new treatments, but they often overlook essential constitutional and functional features of complex human disease. An optimal animal model for human diabetic nephropathy should be affordable, simple to maintain, and easily accessible for practical reasons. Research on mice has made a significant contribution to our knowledge of human biology, physiology, hormones, and medicine. Animal models are used to study various diseases, such as systemic inflammatory illnesses, rheumatic arthritis, seizures, Alzheimer's disease, cardiovascular diseases, atherosclerosis, diabetes, and many more. There are numerous rodent models available for studying the pathogenesis of Diabetes kidney disease (DKD) and evaluating cutting-edge treatment approaches. Throughout this article, we focus on providing a detailed analysis of the animal models currently in use for diabetes nephropathy, such as the db/db mice model, akita mouse model, OVE 26 mice model, ob/ob mice model, NOD mice model, NZO model, KKAy mice model, WDF rat model, Zucker fatty rat model.

Index Terms **- Diabetes mellitus, Diabetes nephropathy, insulin, hyperglycemia, oxidative stress, Animal model**

1. INTRODUCTION:

1.1. Diabetes:

Diabetes mellitus (DM) is a chronic condition characterised by elevated blood sugar level due to insufficient insulin production or inadequate insulin action. Numerous consequences, including neuropathy, nephropathy, retinopathy, and an elevated potential of coronary heart disease, can result from chronic hyperglycemia (King 2012). Due to its numerous consequences, Diabetes mellitus (DM) is a metabolic disorder that causes illness and death by affecting the endocrine system (Omoboyowa et al. 2020).

Fig 1: Mechanism of Diabetes Mellitus

Various types of diabetes are there:

1. Type 1 diabetes mellitus or insulin-dependent diabetes.
2. Non-insulin dependent diabetic mellitus (NIDDM), often known as type2 diabetes
3. Reduced fasting glucose levels (> 126 mg/dL) and diminished tolerance to glucose (> 200 mg/dL after 2 hours of 75g of glucose ingestion).
4. Pregnancy-related diabetes (only during pregnancy) (Kumar et al. 2013).

Diabetes is a main reason of death that will be a significant leading cause in the future. Its increased prevalence in both cities and small towns is a critical public health problem since it can cause a variety of microvascular and macrovascular disorders due to urbanisation, genetic susceptibility, and lifestyle changes (Daniel et al. 2022).Traditionally, diabetes has been diagnosed when fasting blood glucose levels are more than 7 mmol/L (126 mg/dL), when any blood glucose level is 11 mmol/L (200 mg/dL) or extreme with symptoms of hyperglycemia, or when a 2 hr oral glucose tolerance test is abnormal (Atkinson et al. 2014). Type 1 diabetes mellitus is characterised by a unique aetiology in comparison to type 2 diabetes mellitus, which is defined by decreased insulin production and impaired insulin sensitivity by the beta cells (Paschou et al. 2018). Diabetes affects 177 million individuals worldwide. This figure is expected to more than double by 2030 (Kumar et al. 2013).

In 2021, diabetes prevalence was greater in urban (12%) than rural (8%) areas, and it was higher in high- and moderately wealthy (11% vs. 6%) nations. It also increased gradually with age (Hoogeveen 2022). The bulk of fatalities take place in low- and middle-income nations, and they are a major factor in early mortality (Sun H et al. 2021). By 2045, it would increase to 10.9% (570 million people) (Saeedi et al. 2019). As per the World Health Organization (WHO), the greatest financial impact of the rise in diabetes cases in India will be felt by the nation, the patients, and the healthcare system. According to a recent survey in India, the average cost of treating diabetes is Rs. 10,000 in urban regions and Rs. 6,260 in rural ones (Anjana et al. 2017).

Type 1 diabetes mellitus (T1DM) is characterised by hyperglycemia, due to the destruction of pancreas islet cells by an inflammatory response. One of the most common metabolic and hormonal disorders in children is type 1 diabetes. T1DM-related

autoimmunity causes beta-cell loss in a large number of patients (70-90%) and is accompanied by the production of T1DM-associated autoantibodies (Known as type 1a diabetes mellitus) (Katsarou et al. 2017). Microvascular and macrovascular problems are the two main chronic consequences of T1D. Incidence of T1D with youth start in the 0-14year age range varies more than 100 times globally (Borchers et al. 2010). T1D prevalence varies by age groups as well. In most cases, with girls typically experiencing the peak age of onset a little sooner than boys (Catanzariti et al. 2009). The MAPK pathway is left alone, which causes the insulin response between the two routes to be out of sync. This puts patients at risk for atherosclerosis, high blood pressure, and/or difficulties with their small blood vessels. Diabetes is caused by impaired insulin sensitivity in the PI3-K pathway (Love et al. 2021).

Fig 2: Diabetes leads to other health complications

Type 1 diabetes is distinguished by the death of insulin-producing cells in the pancreas, a condition known as insulitis (Yu et al. 2000). Especially in new-born babies, insulin autoantibodies frequently develop first (Devendra et al. 2004). Type 1 diabetes mellitus is an autoimmune condition, and it is currently thought that environmental, inflammation, and genetic factors all play a role in its development (Acharjee et al. 2013). Absolute insulin deficiency, rapid start of symptoms, a predisposition to ketosis, and the requirement for supplemental insulin to sustain life define the beta-cell failure in the pancreas leads to the onset of type 1 diabetes mellitus (also known as insulin-dependent diabetes) (Pociot and McDermott 2002).

Type 2 diabetes affects people in different ways. The clinical indication of the disease requires both genetic and external factors. Insulin insufficiency is always the cause of elevated blood glucose level in type 2 diabetes. Decreased insulin-mediated glucose uptake from muscle, heightened glucose synthesis from the liver, and enhanced free fatty acid mobilisation from adipose tissue are all symptoms of insulin deficit (Gerich 1998). Type 2 diabetes mellitus (T2DM) is characterised by dysregulation of glucose, cholesterol, and protein metabolism, which can be caused by an absence of insulin production, impaired insulin sensitivity, or both (DeFronzo et al. 2015).

It is well acknowledged that type 2 diabetes is an outcome of both population ageing and unfavourable environmental aspects of modern life, such as high-calorie foods, inactivity, and sedentary lifestyles, which encourage the development of obesity. Still, 10% of people with type 2 diabetes have average weight, and many fat people never get the disease. This shows that the environment is not the only cause of type 2 diabetes (Staiger et al. 2009). Diabetes type 2 (beta-cell dysfunction and impaired response to insulin). Both lead to high blood sugar levels, which causes irregular weight loss, changes in energy metabolism, excessive urination, compensatory thirst, increased fluid intake, blurred vision, and increased thirst (Lin Y and Sun Z 2010). Type II diabetes, commonly known as non-insulin-dependent diabetic mellitus (NIDDM), affects only adults and is by far the most prevalent kind (80–90%). The elevated glucose and insulin levels seen in type II diabetes are most commonly attributed to this. Diabetes is characterised by a general insensitivity to insulin (Pories and Albrecht 2001). Children, teenagers, and young people are more likely to have prediabetes and type 2 diabetes mellitus (T2DM) (Chen et al. 2012).Type 2 diabetes may be significantly influenced by race, obesity, insulin sensitivity, and other risk factors (Haffner 1998). According to the WHO, diabetes is "a metabolic disease with different causes characterised by chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism due to problems with insulin production, insulin action, or both" (Ozougwu et al. 2013).

1.2. Diabetic nephropathy:

1.2.1. Introduction and pathogenesis:

Diabetic nephropathy is one of the serious complication side effects of this metabolic disorder. Reactive oxygen species (ROS), which are recognised to be extremely important in the pathophysiology of diabetic nephropathy, are produced as a result of oxidative stress, which is encouraged by hyperglycemia (Alhaider et al. 2011).

Fig 3: Mechanism of Diabetes Nephropathy

It is mostly marked by high blood sugar, or hyperglycemia, which leads to glucose auto-oxidation, glycation of proteins, and stimulation of the polyol mechanism. This causes oxidative injury, which is defined by an increase in the amount of reactive oxygen species (ROS) within cells. An overabundance of ROS causes numerous capillary and macrovascular effects of diabetes, including diabetic nephropathy. (DN) (Sil 2015).

Fig 4: Pathophysiology of Diabetes Nephropathy

Excretion of albumin in urine and glomerular filtration rate estimation are two biomarkers that define diabetic nephropathy (DN). Microalbuminuria is the first stage of DN. Macroalbuminuria (also known as proteinuria or albuminuria) is the next step, then renal failure, and ultimately end-stage renal disease. normo-albuminuria is the name for an elimination rate that falls outside of this range (Ufuoma et al. 2016). Microalbuminuria is defined as UAE between 20-200 mg/min and/or 30-300 mg/24 hr (Jerums and Maclsaac 2002). It is considered to be both an independent marker for cardiovascular illnesses and the earliest detectable marker of diabetic nephropathy. Macroalbuminuria is the loss of more than 300 mg of albumin in a 24-hour urine sample. It is yet the most common criteria for diagnosing and rating DN and is the principal risk factor for nephropathy (Shahwan et al. 2019). One of the common problems that comes up with diabetes mellitus, diabetic nephropathy is characterised by extracellular matrix accumulation in the tubular inter-stitium and glomerular mesangium, capillary and tube enlargement of the kidneys, basement membrane swelling, and glomerular hyperfiltration (Mensah-Brown et al. 2005). This disease typically occurs along with macrovascular disease, such as cardiovascular, cerebrovascular, and peripheral arterial diseases, along with generalised microvascular disease. Compared to diabetics without nephropathy, DN patients have a higher chance of mortality, predominantly due to coronary complications (Satirapoj and Adler 2014).

Early alterations of DN include glomerular hypertrophy, a minor mesangial enlargement (matrix), and expansion of the glomerular capillary walls. The electron microscope makes these alterations more obvious (Soler et al. 2012). The early circulatory changes that take place during DN are induced by a number of different factors, including prostaglandins, nitric oxide, growth hormone, glucagon, angiotensin-II vascular endothelial growth factors, and transforming growth factor (Kaur et al. 2016). For the prevention

of DN, a number of clinical management techniques are advised, including nutritional management, blood glucose management, and blood pressure management (Kundu et al. 2020). The primary cause of end-stage renal disease (ESRD), which is followed by morbidity and mortality, is diabetic nephropathy (DN) (Noshahr et al. 2020). Several variables, including hyperglycemia, obesity, dyslipidaemia, hypertension, and reactive stress, contribute to the progression and worsening of diabetic nephropathy. The majority of these risk factors can be changed. In order to stop and delay the loss in renal function, their careful management is crucial. The importance of managing these risk factors is further evidenced by the fact that many of them are associated with a higher incidence of coronary problems (DN Tziomalos and Athyros 2015). The percentage of diabetic patients who develop end-stage renal disease has decreased as a result of advancements in the management of hyperglycemia and hypertension (Betz and Conway 2016).

1.2.2. Risk factors:

According to research findings over the past five years, oxidative stress, inflammation, and fibrosis are the main factors driving DN progression, giving us a huge array of possible targets. Reactive oxygen species (ROS) build-up results in oxidative stress, which can affect normal cell activity. Chronic hypoxia, a major contributor to DN, causes a series of anomalies in oxygen metabolism in the kidneys of people with diabetes, including reactive stress, nitrosative stress, advanced glycation, carbonyl stress, and endoplasmic reticulum stress (Ahmad 2015).

Fig 5: Risk factors for Diabetes Nephropathy

DN affects around 30% of persons with type 1 diabetes and 40% of people with type 2 diabetes A clinical diagnosis of DN is made when there is protein in the urine, the estimated glomerular filtration rate (eGFR) goes down, and the person has had diabetes for a long time (Chen et al. 2021). DM is different because it can cause both microvascular and macrovascular problems. Microvascular complications are known to cause 25–40% of chronic kidney disease (CKD), also known as diabetic kidney disease (DKD), which is now the leading reason of kidney failure worldwide (Pelle et al. 2022). DKD is the most prevalent cause of ESRD worldwide, accounting for 40% of newly found patients requiring renal replacement treatment. (RRT) (Barutta et al. 2021).
The newly identified coronavirus disease 2019 is caused by SARS-CoV-2. (COVID-19). This pathogen was isolated for the first time in December 2019 (in Wuhan), has already spread all over the globe, creating a serious health crisis on a global scale. The respiratory system is the primary target of the sickness (Elbarbary et al.2020). Patients with infections other than SARS-CoV-2 also have a higher chance of getting diabetes. The length of time that diabetic patients spent in the hospital was much greater than that of the non-diabetic control group (Schiller et al. 2021). For individuals with diabetes who also had any organ consequence from their condition, the risk of dying from a COVID-19 infection was much higher. Importantly, more than 70% of individuals who had formed diabetic nephropathy or who were obese and diabetic did not make it. Patients infected with COVID-19 who also suffered from diabetic nephropathy and diabetes retinopathy had a worse prognosis than those who suffered from simply diabetes and hence required more intensive therapy (Sonkar et al. 2022).

1.3. Animal model:

Animal models can be used to investigate the pathophysiology of the illness and test potential new treatments. However, the majority of models fall short in recapitulating crucial structural and functional aspects of advanced human disease, which limits their usefulness in DN research. This may help explain why treatments that have been effective in animal models have often been less effective in treating DN in humans (Betz and Conway 2016). Live animal research is required to better understand how diseases manifest and propagate throughout the body as well as to find new and improved methods for their detection and treatment (Workman et al. 2010). Animal studies, which are almost exclusively carried out on mice, are crucial for understanding complex disease processes, but they should only be used when all other sources of information, such as disease cell lines, have been exhausted. Before any trials of novel pharmaceuticals may be tried in people, regulatory agencies also require animal investigations. Preclinical animal research is necessary for toxicological evaluations and to support the approval of human drugs (Vandamme 2014).
An optimal animal model for human diabetic nephropathy would allow for DNA research and display many of the tumours seen in people with the disease. Such an animal model should be affordable, simple to maintain, and easily accessible for practical reasons (Alpers and Hudkins 2011). Since the animals share a lot of hereditary and metabolic traits, mice are used as model creatures in research on human biology. Despite their evolutionary relatedness, mice and humans have developed in and gotten accustomed to quite diverse environments, making them into very different animals (Perlman 2016). Mice frequently react to experimental interventions in startlingly different ways than people do. The technologies for making transgenic, knockout, and knock-in mice have given mouse research more momentum and sophisticated tools, and they have increased the use of mice as model organisms dramatically. Research on mice have made a significant contribution to our knowledge of human biology (Birney et al. 2002).
Most of what we know about human biology, physiology, hormones, and medicine comes from study done on animal models in the past. The following five groups—of which the first three are numerically the most significant—can be used to conveniently classify disease models:

- Induced (experimental) models
- Spontaneous (genetic, mutant) models
- Genetically modified models
- Negative models
- Orphan models

If an animal exhibits the same symptoms as people and develops the ailment in the same way, the animal may be used as a homologous model (Hau 2008). Systemic inflammatory illnesses, rheumatic arthritis, seizures, Alzheimer's disease, cardiovascular diseases, atherosclerosis, diabetes, and many more can be mimicked in animal models because of their similarities to human disease. The model is also important for study on bone and joint regeneration, wound repair, tissue engineering, drug development, vascular surgery, surgery to regrow spinal discs, and the effectiveness of drugs and the creation of medical devices (Mukherjee et al. 2022). In order to study long steady DN and measure important hemodynamic and biochemical markers, the best animal model for DN

studies in type 2 diabetes would seem to have human-like structure, physiology, and blood flow in the kidneys (Soler et al. 2012). There are numerous rodent models available for studying the pathogenesis of DKD and evaluating cutting-edge treatment approaches. Increasing total GFR, moderate albuminuria, and mesangial enlargement are the only early characteristics of human DKD that the majority of these models display (Sembach et al. 2021).

1.4. Models:

1.4.1. db/db mouse model:

The db/db rodent was discovered in the United States in 1966 (Sharma et al. 2003). The autosomal recessive mutation found at the Jack-son Laboratory in Bar Harbor, Maine, is the source of the diabetes (db) mouse strain. The C57BL/KsJ strain of mice underwent this spontaneous mutation. Therefore, it is not surprising that the diabetes rodent (C57BL/KsJ db/db) routinely gets a serious diabetic condition like to that of the C57BL/Ks] ob/ob mice, characterised by a rapid onset of hyperinsulinemia, followed by rising glucose with hypo-insulinemia, weight loss, and premature mortality. In comparison to other obese mutants, this strain has a higher prevalence of diabetes (Mao et al. 2006). The most popular mouse used to simulate diabetic nephropathy in Type II diabetes conditions is the db/db mouse model of leptin deficit. Type II diabetes, insulin resistance, and obesity are all made more likely by a leptin shortage. The leptin receptor has been deleted in db/db mice, and their genetic background predisposes them to diabetes consequences such nephropathy (Susztak et al. 2006).

Male mice have diabetes that is more severe than female mice. The LepRdb/db mutant was initially discovered in the C57BLKS/J breed of mice because it greatly increases diabetic nephropathy in that strain. It was then altered by adding DNA from the DBA/2 type, which has characteristics similar to those seen in human diabetic nephropathy (Kitada et al. 2016). The early stage DKD pathology is shown by the db/db mice. C57BLKS/J is a rodent breed that is a cross between the C57BL/6 J and DBA/2 J. It incorporates DNA from many different mouse types and serves as the genetic foundation for the db/db type (Østergaard et al. 2017). In db/db mice, activating mTOR is known to cause kidney enlargement, matrix build up, fibrosis, and renal failure (Susztak et al. 2017). db/db mice are a good and significant model to study how diabetic nephropathy happens because its symptoms are similar to those of diabetic kidney disease in humans (Mao et asl. 2006).

The db/db mouse, a rodent model of genetic diabetes, contains a mutant version of the leptin receptor and, between 5 and 8 weeks after birth, elevated blood glucose level in conjunction with insulin resistance and obesity develops. After 10–20 weeks of persistent hyperglycemia, significant renal pathology is observed, including glomerular mesangial expansion, accumulation of mesangial matrix invading the healthy capillary network, a decrease in creatinine clearance, and an increase in serum creatinine concentration (Østergaard et al. 2017). Since these kidney morphological and functional abnormalities are similar in development and character to those observed in human diabetes, the db/db rodent may be useful for studying the pathogenetic effects and therapeutic interventions of type II diabetes nephropathy (Kitada et al. 2016). A G-to-T point mutation in the leptin receptor is encoded by the db gene, which results in aberrant leptin receptor splicing and dysfunctional signalling. Absence of leptin signalling in the hypothalamus will result in obesity and chronic hyperphagia, which will raise leptin and insulin levels (Sharma et al. 2003). This leptin receptor variation (LepRdb/db) causes improper translation and a dysfunctional receptor for leptin, a hormone generated by adipocytes. This defect causes the hypothalamus to respond abnormally, leading to overeating, obesity, high blood fat levels, high insulin levels, insulin resistance, and eventually diabetes. Db/db mice experience the emergence of overt diabetes followed by progressive kidney damage that resembles human diabetic nephropathy (Tesch and Lim 2011).

1.4.2. Akita mice model:

The Ins2Akita mouse (also known as the Akita mouse) is a hypo-insulinemic diabetic rodent that is not fat. This diabetic strain displays severe hyperglycemia as early as 4 weeks of age and contains an Akita mutation in the insulin 2 gene that changes cysteine 96 to tyrosine. Akita mice do not, however, develop overt-DN because of their C57BL/6 genetic background (Fujita et al. 2009). The newly discovered insulin-2 Akita (Ins2Akita) mouse variant used to study type 1 diabetes could be used to prevent the tissue injury that can happen in the STZ induced of type 1 diabetes model. The mice in this study lose cells from their pancreas due to improper folding of insulin2, which results in cell-selective proteotoxicity. Research has shown that this model is insulin sensitive, even though it was first called a model of diabetes that starts in young adults and gets worse with age (Breyer et al. 2005). First, involvement of a single gene can rule out the possibility of complex genetic traits for diabetic nephropathy. Second, blood glucose levels in male diabetic mice exceed 500mg/100ml (27.8mM) from 8 weeks of age, while female diabetic mice only experience mild dialysis. Because of these factors, the akita mouse is an appropriate subject to analyse the pathological effects of diabetes on the kidneys (Haseyama et al. 2002). To date, only heterozygotes with sporadic type 1 diabetes have been detected in the Akita mouse due to a change in the insulin-2 locus. When compared to heterozygous mice of a similar genetic background, these animals have greater blood sugar levels, more severe albuminuria, and mesangial sclerosis (Yu et al. 2012). With the initiation of hyperglycemia, Akita mice experience progressive renal and retinal failure, characterised by elevated proteinuria, increased vascular permeability, elevated apoptosis, and changes in the retina (Breyer et al. 2005). The non-obese, black-haired C57BL/6 variant mouse discovered in an Akita colony (Akita, Japan) that develops diabetes on its own at an early age demonstrates the autosomal dominant mode of transmission. MODY4 diabetes gene was discovered on chromosome 7 near D7Mit189 in Akita mice (Fujita et al. 2009).

Moreover, Akita mice exhibit echocardiographic indications of heart failure and develop hypertension, which are issues frequently linked to diabetes in people (Tomino and Gohda 2015). Akita mice keep the Ins2/C96Y mutation, with one nucleotide alteration in the Ins2 locus. This variant causes type 1 diabetes by impairing insulin protein structure, leading to harmful injury to pancreas b cells and an impaired ability to produce insulin. Podocyte loss, at least in part due to enhanced apoptosis, is present at an early stage in the progression of diabetic nephropathy (Yu et al. 2012).

Ins2Akita/diabetic mice of varying genetic origins have been phenotyped, and their highly variable kidney histopathology is consistent with the idea that tumours are at an early stage of development (6 months). Gender differences appear to have far less

pronounced effects. Even though nephropathy is generally less severe in women than in men, this could be because women's blood glucose levels are lower, or because their body weight or food intake is different. This has been seen in many animal models of diabetes (db/db and Ins2Akita/) (Gyurko et al. 2006). Albuminuria is an unusual discovery, and male rodents had substantially higher glucose compared to female mice with respect to non-diabetic controls. Male Ins2Akita mice along with diabetic nephropathy have mild high blood pressure, more kidney damage, and albuminuria than male wild-type C57BL/6 mice given STZ (Haseyama et al. 2002). Modest albuminuria and minor structural alterations, such as an increase in the mesangial matrix, thickening of the glomerular basement membrane, and a decrease in podocytes, were seen in the C57BL/6 strain of Akita diabetic mice. These alterations were likely caused by an increase in apoptosis. Oxidative stress and inflammation, both of which have been well-known in the kidneys of Akita Ins2+/C96Y C57BL/6 mice, are hallmarks of diabetic nephropathy. However, the level of albuminuria and organ alterations in Akita altered mice depend on their genetic make-up (Tomino and Gohda 2015).

1.4.3. OVE 26 mice Model:

The OVE26 mouse exhibits Overexpression of calmodulin by genetic means in pancreatic beta cells, which cause inadequate insulin production and Type I diabetes. In mice with an FVB genetic background (The Jackson Laboratory, Bar Harbor, ME), calmodulin overexpression causes severe nephropathy with pronounced albuminuria. Increased mesangial matrix is a hall-mark of nephropathy in these rodents, which can progress to more severe outcomes like widespread glomerulosclerosis, decreased podocyte numbers, and mild kidney fibrosis. The reduced podocyte quantity, albuminuria, and mesangial matrix development seen in these rodents makes them a valuable research tool for studying diabetic nephropathy (Teiken et al. 2008).

The offspring of male heterozygous OVE26 diabetic mice and female wild-type FVB mice develop serious albuminuria by the age of 2 months. At 9 months of age, albuminuria is clearly elevated if the normal urinary albumin output is greater than 15 mg/24 hours. The glomerular filtration rate (GFR) of OVE26 mice considerably rises between the ages of 2 and 3 months, declines between the ages of 5 and 9, and is significantly lower in diabetic mice at the age of 9 months than in control mice at the same age (Zheng et al. 2011). The OVE26 mice become diabetic during their first week of life, but they may live without insulin for more than a year. Significant albuminuria was present in OVE26 mice by the eighth week of life. Renal fibrosis, mesangial matrix enlargement, global glomerulosclerosis, decreased podocyte numbers, and a rise in albuminuria of more than 10 times are all brought on by excess of calmodulin on the FVB background by the time an infant is 6 months old (Xu et al.2010).

These mice have diabetes from the time they are born, but they are able to live without insulin for well over a year while maintaining a weight that is nearly normal. By the age of two months, OVE26 mice showed considerable albuminuria and noticeable polyuria.By 9 months old, the albumin excretion rate had surpassed 15,000 g/24 hours and had gradually grown with age. In certain diabetic animals, the severe albumin loss resulted in hypoalbuminemia. There was an increase in blood pressure and albuminuria (Teiken et al. 2008). The OVE26 type 1 diabetes model resulted in nephromegaly, albumin in the urine glomerulosclerosis, tubulointerstitial fibrosis, random arteriolar hyalinosis, and the possibility of a lower glomerular filtration rate. (GFR). As a result, the OVE26 mouse is regarded as one of the most current studies on diabetic nephropathy that is most applicable to humans (Xu et al.2010). It has been suggested that OVE26 mice make a great model of DN in type 1 diabetes and they are frequently utilized for this purpose (Zheng et al. 2011). The most advanced albuminuria of all mouse models can be seen in the OVE26 diabetic mouse. Since the whole kidney is immune to isolation stress and purity fluctuations, it was chosen for the initial gene expression experiments (Yang et al. 2011).

1.4.4. Nod (non-obese diabetic) mice model:

The hypo-insulinemic type 1 diabetes model NOD mice develop relatively mild kidney problems. This model has only been applied in a small number of renal studies, though Liu et al. examined the function of glutamic acid decarboxylase antigen and discovered it in these NOD mice's proximal and distal tubules (Allen et al. 2004). This strain was created by Makino and colleagues by the inbreeding of diabetic CTS mice that were initially descended from the JCL-ICR strain of mice (Velasquez et al. 1990). Immunologists first believed that the NOD mouse would be a murine "Rosetta stone" for fast unlocking the mysteries of the etiopathogenesis of type 1 diabetes in humans. As a result, the introduction of NOD mice to diabetes research was accompanied with a great deal of hope. The identification of human homologs using the NOD mouse would enable precise prediction of kids who have a high genetic risk of acquiring type 1 diabetes (Atkinson and Leiter 1999).

Antibody-mediated demise of beta cells occurs spontaneously in non-obese diabetic (NOD) rodents at about five months of age. When diabetes sets in, unlike in the previously stated models, the animals show a total lack of insulin and an unequivocal need for insulin treatment. At days, this model is more frequently utilised to do in-depth research on the immunopathogenesis of the loss of islet cells than to examine diabetic kidney problems (Velasquez et al. 1990). The NOD mouse is thought of as a hypo-insulinemic type 1 diabetes model because it spontaneously develops autoimmune diabetes with traits resembling those of type 1 diabetes in humans. Male NOD mice have a considerably lower rate of verified diabetes than female NOD mice, with the majority of female NOD mice developing the disease by week 40. At the age of 3–4 weeks, NOD mice exhibit the onset of diabetes (Allen et al. 2004). It has been demonstrated that NOD mice develop very little renal abnormalities and spontaneous renal illness with unknown cause. Lymphocytes penetrate the kidney in this animal, but renal tissue injury does not become apparent until after the start of diabetes. Four weeks after the beginning of diabetes in these animals, there have been reports of increased albumin excretion in the urine (Todd and Wicker 2001).

Important hereditary and external risk variables for obesity and diabetes have been identified, in part, by studying the NOD rodent model. The NOD model sheds light on the contributions made by B cells and innate immune cells to the T cell-mediated illness (Pearson et al. 2016). Proteinuria is present in NOD mice at 18 weeks of age, and curiously, males have higher levels of proteinuria than females do. The capillary basement membrane thickening and glomeruli's deposition of material that resembles basement membrane are the only renal abnormalities that are present. Moreover, the mesangium has IgG and IgA deposits (Rüster and Wolf 2010). The 1974 discovery of the NOD mouse led to its subsequent inbreeding. The development of our understanding of disease mechanisms and the application of therapies, such as the use of broad spectrum immune suppressive

regimens tried on patients, have both been facilitated by this paradigm, which has been essential (Reed and Herold 2015). When it comes to animal models, NOD mice are frequently regarded as "the best there is," short of a human study (Atkinson and Leiter 1999).

The non-obese diabetic (NOD) mouse is currently acknowledged as a suitable model for studying the autoimmune exocrinopathy common in people with Sjiigren's syndrome. Similarly, to humans with Sjogren's disease, aged NOD rodents exhibit histopathological changes and, more importantly, clinical symptoms of declining exocrine tissue secretion function. The NOD rodent is a powerful tool for studying the mechanisms behind Sjögren's syndrome and other autoimmune diseases (Todd and Wicker 2001). Advances in identifying genes in congenic groups of the nonobese diabetic (NOD) rodent have made it possible to investigate gene functions and relationships that can be physically represented as intrapathway association on a repeatable basis (Ridgway et al. 2008). Possible long and varying times to acquire diabetes may explain why NOD rodents have not been studied widely in terms of diabetic nephropathy. Many studies on diabetic nephropathy have been conducted using animal models of diabetes brought on by pharmacological means (Reed and Herold 2015). However, a few investigations have shown that NOD rodents may develop kidney illness after developing diabetes. We examined humoral and cellular immunity indicators in NOD mice, which acquire diabetes on their own, to find out if immune responses play a part in the progression of diabetic nephropathy. Glomerulosclerosis appears soon after the beginning of diabetes in nonobese diabetic (NOD) mice (Pearson et al. 2016).

1.4.5. Ob/ ob mice model:

In 1949, the mouse ob/ob model was discovered for the first time in an outbred population at the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, which is located in the state of Maine. It was then transplanted to the colony of C57Bl mice, which had already been created and had a well-established history. Ob/ob mice (OM) were used as a model for diabetes and obesity because they were hyperphagic, obese, hyper insulinemic, and hyperglycaemic (Lindström 2007). Clee and Attie have developed a rodent model of insulin resistance by employing a variety of mice known as BTBR (black and tan brachyuric, also known as short-tailed mice) that contains the ob/ob mutation (Hudkins et al. 2010). In the Jackson Laboratory, where the mutant's initial symptoms of extreme obesity and hyperglycemia were first observed, the mouse's obesity was determined to be an unintentional inherited genetic trait. Afterwards, the (ob) mutation was preserved and spread to many inbred strains. The ob/ob mouse may exhibit various obesity-diabetic syndromes depending on the inbred background. As a result, the C57BL/6J ob/ob mouse strain of the ob mutant exhibits severe hyperinsulinemia linked to pancreatic islet hyperplasia, large obesity, mild glucose intolerance, and transitory hyperglycemia (Hellman 1965).

The fast decline of health in BTBR ob/ob mice used as a diabetic nephropathy model is advantageous because it shortens the time required to perform treatment studies that may alleviate advanced diabetic nephropathy (Hudkins et al. 2010). The ob/ob genetically fat rat has a mutation in leptin itself, as opposed to db/db mutations, which have a genetic change in the ligand of the leptin receptor. The DBA2/J and C57BL/6J lines carry the Lepob gene. Although main research to back up the claim that C57BL/6J ob/ob mice have comparatively modest renal anatomy and function are ambiguous, this claim is supported by some data (Haluzik et al. 2004). The obese hyper-insulinemic mouse is distinct from the db/db mice. Although it lacks leptin, the leptin signalling mechanisms are intact. Ob/ob mice come in two different varieties. One has significant hyperglycemia and -cell atrophy and has a C57BLKS/J genetic background. The other type of mouse that comes from the C57BL/6J line only has mildly high blood sugar and enlarged pancreatic ducts. When ob/ob mice have kidney disease, the changes in their glomerulus are mostly large and lumpy (Hummel et al. 1972). The use of BTBR ob/ob rodents as a model of DN is helpful because, in a brief period of time, these animals acquire several abnormal features of human DN (Haluzik et al. 2004). At 4 weeks, BTBR ob/ob mice started to experience increasing proteinuria. By 8 weeks, glomerular hypertrophy and mesangial matrix build-up, signs of early DN, had already appeared, and by 20 weeks, glomerular lesions resembling those seen in advanced human DN had also appeared. At the 22-week mark, we observed a rise of 50% in the mesangial matrix as well as a rise of 20% in the thickness of the basement membrane. There was focal arteriolar hyalinosis, mesangiolysis, widespread mesangial sclerosis (which was getting close to nodular glomerulosclerosis in some places), and focal mild interstitial fibrosis. Reduction of Podocytes started initially and kept going on (Hummel et al. 1972).

Hyperphagic, fat, hyperglycaemic, and developing type 2 diabetes in rodents with the ob/ob gene depends on the mouse breed background. Furthermore, leptin, an appetite-regulating hormone, is absent in these people. The increasing proteinuria and kidney histopathology observed in BTBR ob/ob mice is extremely prognostic of human DN, making these animals a reliable model of type 2 diabetes (Hudkins et al. 2022). High insulin levels, pancreas islet enlargement, and insulin resistance are the initial symptoms seen in rodents with the ob/ob mutant put onto a BTBR background. Extreme glucose is also present by the time the animals are 6 weeks old. 11–15 Even though the ob/ob mutation causes obesity in both the C57BL/6 and BTBR strains, the C57BL/6 ob/ob mice are insulin resistant but not particularly likely to develop diabetes, while the BTBR ob/ob mice are insulin resistant and more susceptible to the disease (Hudkins et al. 2010).

The leptin-deficient BTBR ob/ob animal is used as a model of type 2 diabetic nephropathy because it displays glucose, obesity, and elevated lipid levels but not high blood pressure (Lindström 2007). Thermal hypoalgesia, cutaneous allodynia, and a 78% loss of intraepidermal nerve filaments were all evident aberrations in the hind-limb digital sense nerve conduction velocity (SNCV) and sciatic motor nerve conduction velocity (MNCV) of ob/ob mice at 11 weeks of age (Hummel et al. 1972). Unlike B6 mice, BTBR ob/ob animals develop serious diabetes, so we inserted the ob mutant into the BTBR strain to raise leptin levels. Even though their glucose levels are only marginally elevated, the majority of female BTBR ob/ob rodents are hyper-insulinemic and insulin resistant at 6 weeks of age (Hellman 1965). Ob/ob mice exhibit metabolic abnormalities that are comparable to type 2 diabetes in people. A shortened form of leptin that is not secreted is the outcome of the ob mutation. Leptin generally promotes satiety and weight maintenance, but both mutations alter how it works (Hudkins et al. 2022). Progressive proteinuria and a renal histo-morphological profile are developed in BTBR ob/ob mice, and these traits are strikingly similar to those of individuals with advanced diabetic nephropathy in humans (Hudkins et al. 2010).

1.4.6. Nzo (newzealand obese mice) model:

The first NZO strain was made by Dr. Franz Bielschowsky at the New Zealand Otago Medical School. He used a group of mice from the Imperial Cancer Research Fund Laboratories in London that had been brought to New Zealand by W.H. Hall in 1930. The NZB, NZO, NZC, and NZW lines were created by Bielschowsky in 1948 by inbreeding and selection for various coat colours. Mice with an agouti colouring were mated with their brothers and sisters to create the NZO variety, which is homozygous at the agouti gene due to inbreeding (Kluge et al. 2012). Type 2 diabetes and a polygenically inherited form of obesity are exhibit in New Zealand obese (NZO) mice. The kidneys exhibit mild microscopy symptoms of both lupus and diabetes-related nephropathies, such as glomerulosclerosis, glomerular growth, mesangial deposits, and minor basement membrane swelling, indicating that they may be more vulnerable to autoimmune disease (Melez et al. 1980).

The NZB (black) variant was developed through the same process of selective inbreeding used to generate this strain: the inbreeding of two agouti mice. Autoimmune diseases are also very common in NZO mice. By the age of six months, NZO mice have renal dysfunction (Velasquez et al. 1990). The New Zealand Obese (NZO) mouse breed has a type of diabetes that is passed down from parent to child. By 24 weeks of age, NZO rats have more signs of kidney degeneration, such as a thickening of the GBM and the growth of the mesangial matrix in a random way (Melez et al. 1980). The NZO type carries a variant of the leptin receptor called Lepr-NZO, which has several altered amino acids. The NZO mouse also has genes that we don't know about yet that make it more likely that islet cells will die, which, along with insulin resistance, can cause hyperglycemia. The NZO mouse is the best way to study the biology of the metabolic condition and figure out which genes are to responsible (Ortlepp et al. 2000).

The strain is characterised by the presence of metabolic syndrome symptoms in people, such as hypertension, dyslipidaemia, and beta-cell dysfunction, which can ultimately result in type 2 diabetes (Kluge et al. 2012). Hyperglycemia and elevated insulin levels occur as early as 8-12 weeks in male NZO rodents with type 2 diabetes. Serum insulin levels drop afterward, which has been related to beta-cell mortality. The condition is caused by many genes, and previous study used outcross offspring of the strain and the creation of sub-congenic lines to find genes linked to fat, high cholesterol, and high blood sugar (Joost and Schürmann 2014). The New Zealand Obesity (NZO) mouse has been suggested as a potential model for autoimmune diabetes. NZO rats get fat, can't handle glucose, are resistant to insulin, and have low-titer IgM antibodies that attack the insulin receptor. It has been shown that they have antibodies in their blood against both their own DNA and single-stranded, damaged DNA (Ortlepp et al. 2000). The New Zealand Obesity (NZO) mouse is used as a model for diabetes mellitus type 2 and extreme obesity. We already knew that the NZO mouse type is very sensitive to fat based on a study between a chow diet with 15% fat (of total calories) and a synthetic diet with 45% fat (Melez et al. 1980). Diabetes is poly-genetically acquired in these rodents. They are both overweight and insulin-resistant. These mice have more visible kidney disease, such as GBM thickness, exudative lesions, and extensive and irregular swelling of the mesangial matrix (Joost and Schürmann 2014).

1.4.7. KKAy mice model:

This variety was initially produced at the Takeda Chemical Corporation in Osaka, Japan, from black KK females and yellow KKAy males. The KK mouse only has the diabetic gene, whereas the yellow obese and diabetic genes are present in this animal. Obese KKAy mice have early onset, severe hyperinsulinemia, and hyperglycemia. Renal involvement is unique among diseases because of how quickly it progresses and how quickly it becomes evident after only three months. This is in opposition to what is seen in other rodent models of diabetes, where GBM gradually thickens over time (Diani et al. 1987). The KKAy mouse is a hyper-insulinemic model with only minimal renal disease, modest GBM thickness, and diffuse glomerulosclerosis (Allen et al. 2004). They have obesity and a modest form of insulin resistance, which male mice exhibit more severely than female mice. About 10 to 15 weeks of age, KK mice begin to experience albuminuria, but the causes of this condition are still not completely understood (Matsumoto et al. 2008).

The KKAy mice were produced by mating a golden male Ay mouse with a black KK female mouse carrying a mutant variation of the agouti gene, resulting in both parents being fat. Obesity, high levels of lipid insulin resistance, and insulin deficiency are all notably present by the age of 8 to 12 weeks in this breed. Diabetes in mice can be seen as early as 4 weeks old as widespread glomerulosclerosis, irregular nodules, and significantly higher albuminuria. As the disease gets worse, these changes become more severe (Diani et al. 1987). KKAy/Ta rodents are an excellent paradigm for studying type 2 DN because the kidney injury they experience is highly similar to that of people with DN. The albumin to creatinine ratio (ACR) in mouse pee increases between weeks 8 and 12. Around 16 weeks of age, KKAy/Ta animals show signs of proliferative glomerulonephritis, characterised by glomerular hypertrophy and extracellular mesangial matrix (ECM) (Matsumoto et al. 2008). Pathogenic alterations such as a thickened glomerular basement membrane and an enlarged mesangial matrix are evident in KKAy/Ta mice and early-stage diabetic nephropathy in humans. At 8 weeks of age, the albumin to creatinine ratio (ACR) in the urine of diabetic KKAy/Ta rats is 250-350 mg/g Cr, and by 16 weeks of age, it has increased to 550-600 mg/g Cr. Therefore, KKAy/Ta mice have been suggested as a good model for the beginnings of type 2 diabetic nephropathy (Zhang et al, 2006).

1.4.8. Wistar diabetic fatty (WDF) rat model:

The Wistar fatty rat was created by introducing the fatty (fa) gene from the Zucker rat (13 M strain) into the Wistar Kyoto rat. It is a hyperglycaemic, naturally fat rodent. After five generations of backcrossing, the Wistar fatty (fa/fa) rat gets obesity, high insulin levels, glucose intolerance, high levels of lipid and hyperphagia similar to Zucker rats. Male rats begin to exhibit hyperglycemia, polydipsia, and glucosuria as early as week 8 and their symptoms get worse as they age (Ikeda et al. 1981). Albuminuria and a lower GFR emerge in Wistar obese rats with kidney illness at 20 weeks of age. Kidney growth and capillary thickening are observed between the ages of 20 and 42 weeks. In 42-week-old Wistar fatty rats, the spherical and mesangial volume, as well as the surface area and thickness of the GBM, are all much greater than in lean control rats (Kava et al. 1989). In the later stages of diabetic nephropathy, WF rats with kidney damage caused by diabetes have intermediate to serious glomerular lesions and severe tubulointerstitial fibrosis. So, WF rats may be a good way to study type 2 diabetes with end-stage kidney disease on an animal level. Unlike people who have diabetic nephropathy, WF rat kidney do not show signs of mesangial tumours or mesangiolysis (Ikeda et al. 1981).

Ikeda et al. (1981) made Wistar diabetic fatty (WDF/Ta-/a) rats to serve as a model for diabetes that doesn't need insulin. (NIDDM). In this model of gender different NIDDM expression, only the fat WDF/Ta-/a men showed signs of diabetes. Male WDF/Ta-/a rats fed standard lab food developed glucose, hyperinsulinemia, and decreased insulin sensitivity; likewise, female WDF/Ta-/2 rats fed a high-sucrose diet or administered a 30% sucrose solution developed the same metabolic abnormalities (Kava et al. 1989). Wistar diabetic fatty rats are a new type of rats that are genetically fat and also have the fa gene. This strain was created by mating the Zucker rat's fa gene to the Wistar-Kyoto strain background, which has a slightly carbohydrate intolerance. Plasma levels of insulin and glucose are normal in lean WDF rats. Nonetheless, plasma glucose levels are noticeably raised in obese male WDF rats (Turkenkopf et al. 1991). The male obese Wistar Diabetic Fatty (WDF) rodent has been used as a hereditary model for both obesity and non-insulin dependent diabetes (NIDDM) (Greene et al. 1994).

1.4.9. Zuker fatty rat model:

Historically, hyper insulinemic obesity has been modelled on the Zucker fatty rat. Obesity arises at a young age and is caused by a single autosomal recessive (fa) gene (Mega et al. 2011). The Wistar Kyoto rats, who have insulin resistance and a leptin-receptor mutation, were crossed with obese Zucker fa/fa rats to create the Zucker diabetic fatty rats (ZDF) (Al-Awar et al. 2016). A single autosomal recessive gene, f a, causes obesity in the fatty Zucker rat. Hyper insulinemic but euglycemic has been widely described for the obese (falfa) rat. In 1978, Dr. Walter Shaw of the Eli Lilly Company provided breeding pairs that were used to start a colony of Zucker rats in the Diabetes Research and Training Centre at Indiana University School of Medicine (Clark et al. 1983). These rodents develop diabetes as their beta-cell mass decreases. Gluco/lipo-toxicity may be responsible for the absence of beta-cell mass development. In this model, diabetes manifests as early as 8 weeks of age, accompanied by decreased glucose tolerance and insulin secretion, while albuminuria is marginally elevated in male ZDF rats at 6 weeks of age. As early as 16 weeks of age, ZDF rodents develop DN, which is characterised by substantial proteinuria and glomerulosclerosis. 10 weeks after birth, ZDF rats and mice develop significant albuminuria (Coimbra et al. 2000).
A homozygous nonsense variation in the leptin receptor gene is what makes Zucker fat (ZF) rats fat. (Lepr). Zucker diabetic fatty (ZDF) rats, which are linked to ZF rats but are overweight and show signs of diabetes, are often used to study Type 2 diabetes (Shiota and Printz 2012). A change in the Zucker diabetic fatty (ZDF) rat's leptin receptor (fa/fa) gene causes obesity, insulin resistance, decreased glucose tolerance, high blood pressure, renal and coronary heart disease, and other conditions similar to those seen in people with T2DM, such as diabetic nephropathy (Mega et al. 2011). This breed of rats was discovered in 1961 as a result of a Merck (M-strain) and Sherman rat hybrid. By the time the rats are 4 weeks old, they are obese due to a mutant leptin receptor that causes hyperphagia. These rats exhibit poor glucose tolerance in addition to being hyper insulinemic, hyper lipidemic, and hypertensive. When fed a high-calorie rodent diet, male rodents with a homozygous variation (fa/fa) of the leptin hormone receptor develop type 2 diabetes. By the time they are 10 or 11 weeks old, these rodents have developed diabetes, with typical feeding-state glucose levels of 500 mg/dL having been seen as early as the ages of 3 and 8 due to substantial insulin resistance and glucose intolerance (Al-Awar et al. 2016). Because of insulin intolerance, glucose sensitivity, and diminished pancreatic cell function, homozygous male ZDF rats for the fa gene variation acquire full-blown diabetes as they grow. Male ZDF mice are frequently used as a genetic model for the illness due to their parallels to humans with obesity-related type 2 diabetes. The parallels between type 2 diabetes and weight are the main emphasis of our discussion of this theory (Coimbra et al. 2000). The Zucker diabetic fatty (ZDF) rat is an NIDDM rodent model in which obese purebred males develop diabetes (Shiota and Printz 2012).

DIET INDUCED DIABETES NEPHROPATHY RODENT MODELS: (Preguiça et al. 2020, Deji et al. 2009) [Table -1]

2. CONCLUSION:

In our article, we discussed about various animal models for assessing diabetes nephropathy like the db/db mice model, akita mouse model, OVE 26 mice model, ob/ob mice model, NOD mice model, NZO model, KKAy mice model, WDF rat model, Zucker fatty rat model. Live animal research is essential to better understand how diseases manifest and propagate, and preclinical animal research is necessary for toxicological evaluations and to support the approval of human drugs. The C57BLKS db/db mice are a common DN model for type 2 diabetes, but they only have mild DN, moderate albuminuria, and mesangial matrix thickening. The Wistar fatty rat (fa/fa) was made by moving the fatty (fa) gene from the Zucker rat (13 M strain) to the Wistar Kyoto rat. These rats are a freshly developed genetically fat breed with the fa trait. The Zucker fatty rat, which is produced by a single inherited recessive (fa) trait, has traditionally been used to mimic hyper-insulinemic obesity. The most important details of the phrases DN evolution, body type, and function are that DN evolution can cause a range of symptoms, including increased calorie intake, changes in proteinuria and blood glucose levels, ovation, mesangial enlargement, glomerular sclerosis, high cholesterol, fructose, and fructose. These symptoms can lead to serious health issues, including end-stage renal disease, severe tubular lesions, and increased urine volume and renal function indices. This Review covers the present research in the area of diabetes nephropathy studies using the animal model, and explain why it is useful.

Abbreviations: DN: Diabetes Nephropathy, T2D: Type 2 Diabetes, DKD: Diabetes Kidney Disease, DM: Diabetes Mellitus, NIDDM: Non-insulin dependent diabetic mellitus, WHO: World health organization, T1DM: Type 1 Diabetes mellitus, ROS: Reactive oxygen species, ESRD: End-stage renal disease, GFR: Glomerular filtration rate, CKD: Chronic kidney disease, RRT: Renal replacement therapy, Ins2Akita: Insulin-2 Akita, NOD: Non-obese diabetic mice, NZO: New-Zealand obese mice, ECM: Extracellular mesangial matrix, WDF: Wistar diabetic fatty rat, ZDF: Zucker diabetic fatty rat, SNCV: Sense nerve conduction velocity, MNCV: Motor nerve conduction velocity, HFD: High fat diet

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Conflict of Interests:

"The authors involved in this article have no conflicts of interest to declare. The contents of this article have seen and approved by each co- author, and there are no competing financial interests in the subject matter discussed in this article."

Figures and Tables:

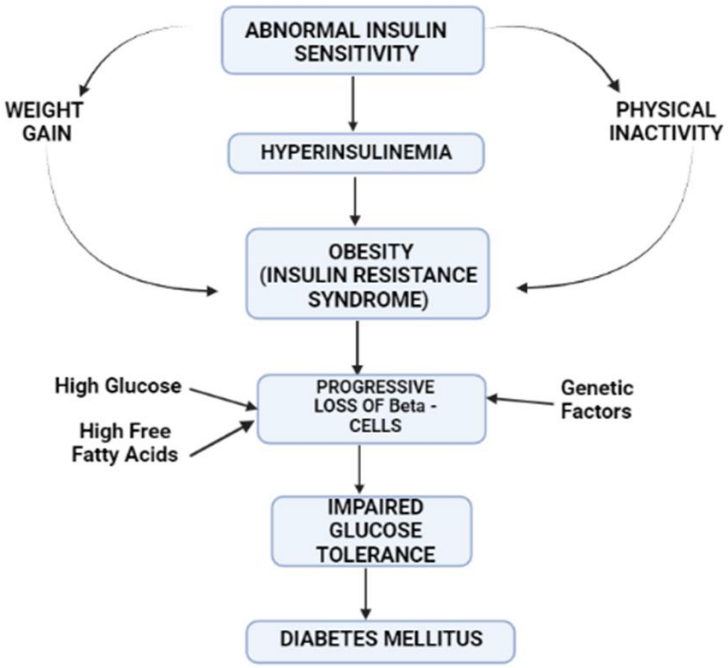

Fig 1: Mechanism of Diabetes Mellitus

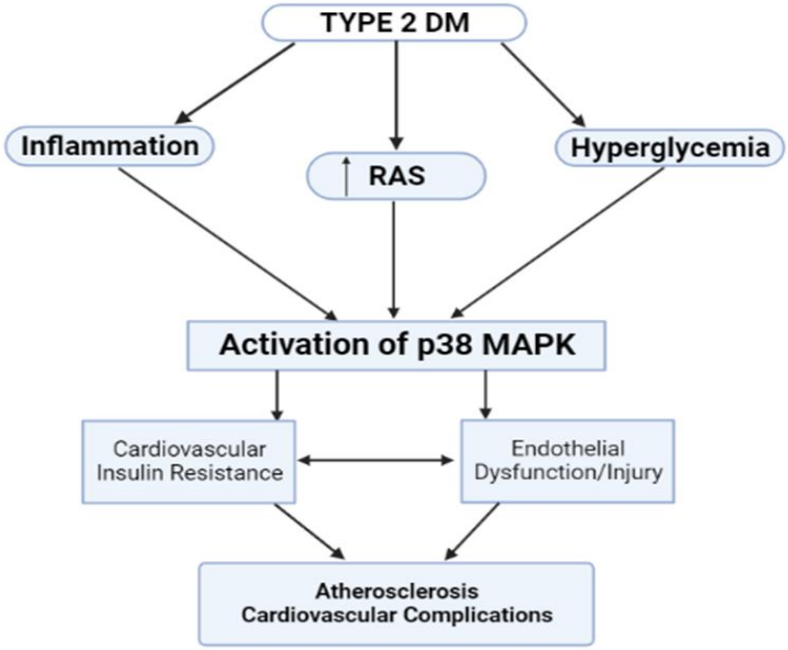

Fig 2: Diabetes leads to other health complications

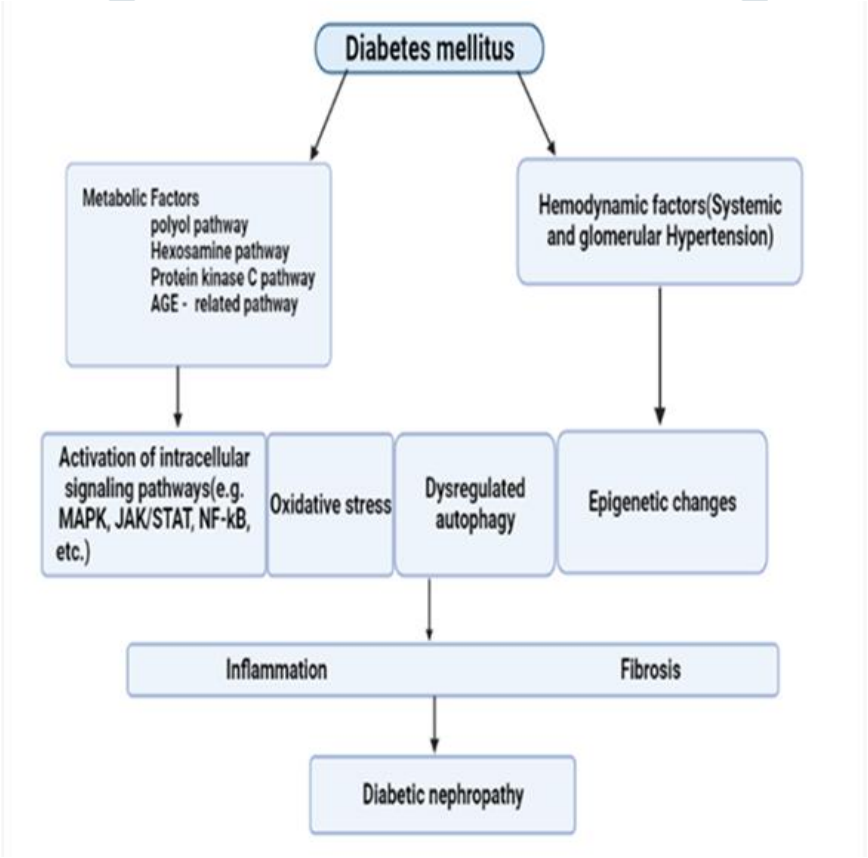

Fig 3: Mechanism of Diabetes Nephropathy

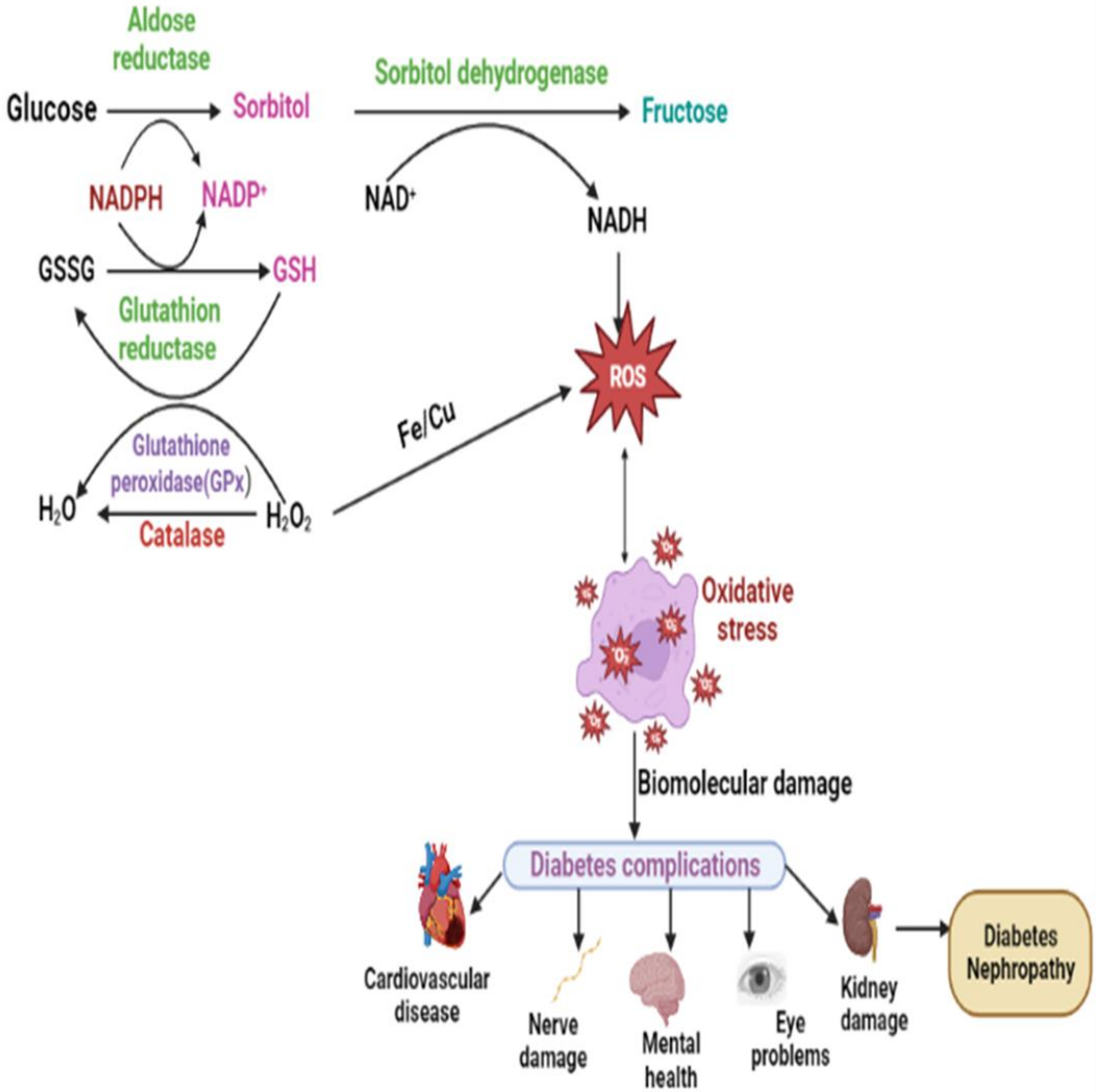

Fig 4: Pathophysiology of Diabetes Nephropathy

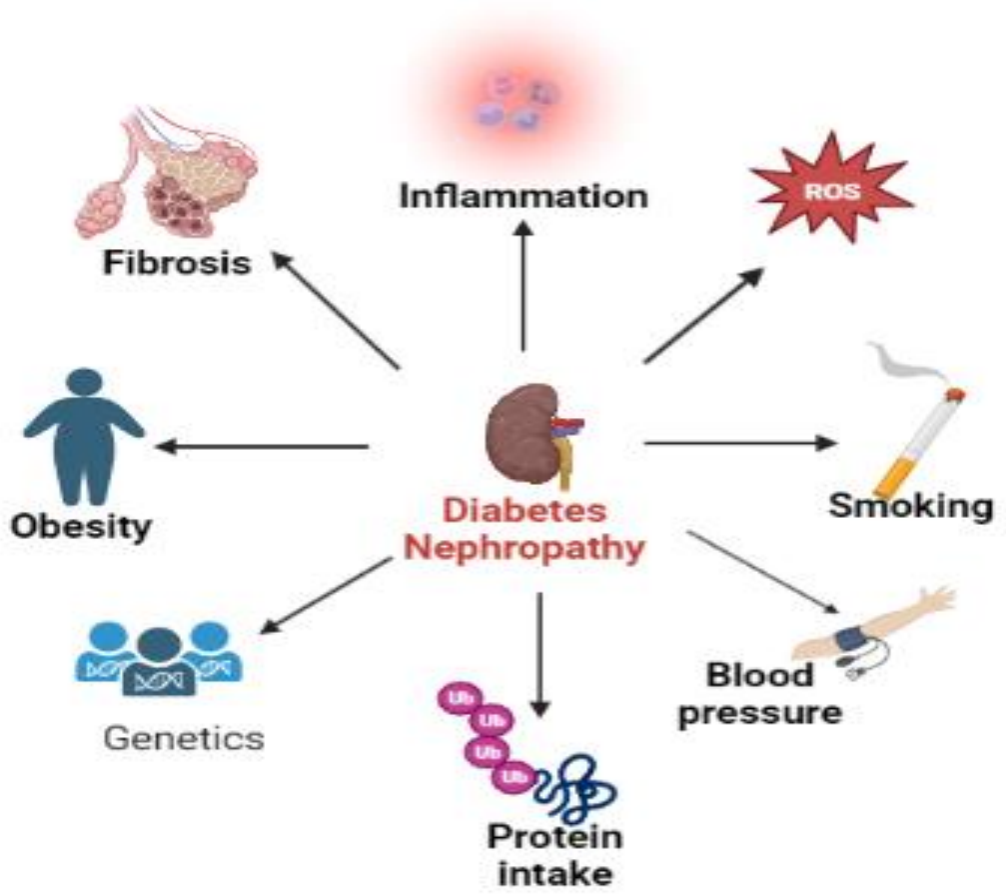

Fig 5: Risk factors for Diabetes Nephropathy

DIET INDUCED DIABETES NEPHROPATHY RODENT MODELS: [Preguiça et al. 2020, Deji et al. 2009]

Table -1

Type of Diet	Composition (%)	Time period (Weeks)	Species	Characteristics of DN
HFD (High fat diet)	30% calories from fat	20 to 28	Rat	Not Able to Achieve Substantial Improvements in kidney Function or Basal Microvascular Blood Flow
	60% calories from fat	12	Mice	Impaired salt management, elevated extracellular matrix protein build-up, and glomerular lesions
HFD + Low dose STZ	60% calories from fat	5	Rat	Higher proteinuria and blood glucose levels are associated with more severe kidney lesions in animals.
	11.3% calories from fat	15 to 25	Rat	Overt proteinuria, mesangial enlargement, and glomerular sclerosis appear after 25 weeks of microalbuminuria and increased creatinine clearance.
High fructose	60% calories from fructose	6 to 8	Rat	Proximal tubule cell growth and hyperplasia; renal hypertrophy; arteriolopathy; glomerular hypertension; constriction of the cerebral vasculature; (focal tubulointerstitial injury)
	66% calories from fructose	4	Rat	kidney lesions such as serious tube lesions, broad and irregular glomerular lesions, and rises in urine volume and kidney function markers are all caused by ageing.
	67% calories from fructose	16	Mice	When the kidneys of C57Bl/6J, CBA/JN, and DBA/2N mice were injured, only the DBA/2N animals developed tubulointerstitial fibrosis.

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