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CURRENT APPROACH IN THE PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

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Abstract

Diabetes mellitus is a chronic and long-standing metabolic disease characterized by increased blood glucose levels. With time, diabetes can cause serious harm to the nerves, kidneys, heart, eyes, and blood vessels. One of the most severe complications of diabetes mellitus is diabetic nephropathy. Different pathophysiological pathways lead to the development of diabetic nephropathy. This review aims to explain the nature, causes, pathogenesis, and treatment strategies of diabetic nephropathy.

1. Introduction

Diabetes mellitus (DM) is a long-standing illness brought on by the body's incapacity to metabolize and control blood sugar, either because the pancreas secretes excess insulin or because insulin cannot regulate blood sugar (1). Diabetes mellitus (DM) is deficit hyperglycemia, insulin production, and/or resistance (2). The beta cells of the pancreatic islets of Langerhans release the polypeptide hormone insulin, which controls blood glucose levels as well as the absorption and utilization of glucose.

Type 1 diabetes (insulin-dependent), type 2 diabetes (non-insulin-dependent), and gestational diabetes (pregnancy diabetes) are the three primary forms of DM (3).

1. **Type 1 diabetes mellitus (T_1DM)** is an endocrine illness where the pancreatic cells cease making insulin, typically due to immune system injury. Insulin replacement is therefore essential to the course of therapy since this causes hyperglycemia and ketosis. Though it can happen at any age, the frequency is highest in adolescence and the early stages of adulthood. Diabetic ketoacidosis is one example of an acute consequence that has to be treated right away. Chronic issues include diseases of the micro- and macrovascular systems (4).

2. **Type 2 diabetes (T_2DM)**: It is the most prevalent form of diabetes, accounting for around 95% of all diabetes cases. It is also known as non-insulin-dependent diabetes. Insulin resistance or insufficient insulin level, the production of insulin in the body, causes the inability to maintain normal blood sugar levels. Lifestyle variables, including obesity, sedentary behavior, and poor food, are frequently linked to type 2 diabetes (5).

3. **Gestational diabetes**: Gestational diabetes is a condition that occurs during pregnancy and affects about 3-9% of pregnant women. Gestational diabetes is characterized by impaired insulin action under the influence of hormones produced by the placenta, which causes blood sugar to rise (6). GDM is a prevalent pregnancy issue that many women experiences. It has been linked to several adverse gestational and fetal outcomes. Furthermore, GDM resolves after delivery, but women who suffer from the condition have an increased risk of developing type 2 diabetes in the future (7).
4. Certain disease types don't easily fall into those categories. Two prominent instances are latent autoimmune diabetes in adults (LADA) and maturity-onset diabetes of the young (MODY). They have specific characteristics in common with types 1 and 2 but also unique symptoms and therapies (8).

2. Complications of Diabetes Mellitus

Years of poorly managed hyperglycemia in diabetes mellitus may result in a variety of problems, most of which are vascular and can damage tiny arteries (microvascular), big vessels (macrovascular), or both.

2.1. Macrovascular diseases Include peripheral artery disease, angina, myocardial infarction, transient ischemic episodes, and strokes caused by atherosclerosis of the big blood arteries.

2.2. Microvascular diseases Include the three prevalent and dangerous complications of diabetes: neuropathy, nephropathy, and retinopathy (9).

2.2.1. Diabetic Nephropathy

Diabetic nephropathy (DN) is a heterogeneous renal disease that is brought on by long-term diabetes and is frequently supported by histological abnormalities. Albuminuria and/or a decrease in the estimated glomerular filtration rate (eGFR) in diabetic individuals are characteristics of diabetic nephropathy DN (10).

Diabetic nephropathy can occur in about 25–35% of type one or type two diabetic patients. When end-stage renal disease is present, the illness's clinical manifestations might include hyperfiltration, microalbuminuria, macroalbuminuria, and nephrotic proteinuria to progressive chronic kidney disease (11).

Some patients with diabetic mellites (DM) remain not diagnosed for years because they do not have screening or laboratory tests. Also, diabetes may take several years before affecting renal function (12).

Chronic kidney disease (CKD) from diabetes or other causes is operationally defined as kidney structural or functional abnormalities that have been present for more than three months, have health concerns, and necessitate one among two established or deduced standards for >three months: either eGFR <60 mL/min/1.73 m2 or other indicators of renal impairment, such as albuminuria. The albuminuria level is characterized as albuminuria that persists or exceeds 30 mg/g. (>300 mg/24 h) overextended measurements lasting three months or longer regardless of eGFR (13).

2.2.1.1. Etiology

Long duration of uncontrolled diabetes can lead to damage to renal vascular clusters, causing kidney damage and increasing blood pressure. Hypertension can cause more kidney damage by increasing the pressure on the renal glomerulus (14).

2.2.1.1.1. Hypertension

High blood pressure is an independent risk factor for the progression of nephropathy among patients with diabetes. Hypertension is twice as common in diabetic patients as it is in the general population. In individuals with type 1 diabetes, hypertension usually develops as a result of microalbuminuria or nephropathy, but in patients with type 2 diabetes, hypertension usually develops before renal impairment. According to a survey, 58–70% of individuals Having type 2 diabetes that was just discovered were already having hypertension (15). The renin-angiotensin-aldosterone system (RAAS) is stimulated in people with diabetes, which results in salt-water retention and volume expansion from increased renal sodium reabsorption, which reduces the number of vasoactive chemicals (16).

2.2.1.1.2. Obesity, Hyperuricemia and Dyslipidemia

While the National Kidney Foundation and other organizations advise overweight type 2 diabetes people to lose weight (17), further research is required to determine the connection between obesity and chronic kidney disease (CKD). According to some research, a greater body mass index (BMI) has little bearing on how quickly type 2 diabetics' CKD progresses (18). However, a different study involving patients with advanced Diabetic nephropathy (DN) revealed that a brief, strict weight-loss program significantly lowers serum creatinine and cystatin C concentrations by 12% (19).

A higher blood uric acid level is linked to a quicker course of Diabetic kidney disease (DKD) (20). According to the findings, individuals with type 1 diabetes mellitus are more likely to acquire micro- or macro-albuminuria for every 1 mg/dL rise in baseline serum uric acid throughout a 6-year follow-up (21). This indicates that hyperuricemia is a good predictor of the development of albuminuria in these patients. These were supported by different research that found that treating the metabolic syndrome was linked to a reduction in the rate at which individuals with type 2 diabetes mellitus developed renal impairment. (22).

An advanced trial included 11140 individuals with type 2 diabetes who were followed up for five years. Reduced baseline levels of high-density lipoprotein (HDL) cholesterol were linked to a markedly elevated chance of developing micro- and macro-albuminuria and cardiovascular events. Additionally, research revealed that lower HDL cholesterol levels may raise the risk of a higher creatinine level and renal disease-related mortality, but this relationship was not statistically significant (23). According to Chang et al.'s research, individuals with type 2 diabetes who have greater HDL levels are less likely to develop diabetic nephropathy (24).

Treatment for dyslipidemia with statins (drugs that decrease cholesterol) has been demonstrated in randomized controlled studies to preserve renal function (25) potentially.

2.2.1.1.3. Other Risk Factors

Other risk factors include:

Smoking: smoking may increase the level of inflammation and may lead to hypertension, which may increase the incidence of renal damage.

Age: Increased age leads to a decrease in GFR, especially (above 65 years).

Sex: Female is more susceptible to developing DN

Race: Diabetic nephropathy DN is more common in African Americans, Native Americans, and Asian Americans (26).

These factors for DN may be separated into two categories: modifiable and non-modifiable variables. Smoking, hypertension, hyperglycemia, and dyslipidemia are examples of variables.

Race, age, gestation, genetic profile (family history of developing DM), and sex are non-modifiable risk variables (27).

Numerous mechanisms and triggers, including oxidative stress, angiotensin II (Ang-II), and inflammatory processes, have been implicated in the onset and development of diabetic kidney disease (DN) (28).

3. Pathophysiology of Diabetic Nephropathy

The result of prolonged uncontrolled hyperglycemia is renal nephron death. This appears as glomerulosclerosis, interstitial fibrosis, and tubular atrophy. After years of renal micro- and macroscopic changes, fibrosis is the endpoint resulting from diabetic mellites.

Higher osmolality in the glomerular capillaries brought on by hyperglycemia raises glomerular pressures. Because of the enhanced glomerular filtration caused by this action, the eGFR reading is deceptively low to normal due to increased creatinine filtration in the presence of hyperglycemia (29). This hyperfiltration may be multifactorial, as proposed. Chemokines and enzymes like ornithine decarboxylase produce renal enlargement, characterized by increased filtration surface area per nephron released in response to hyperglycemia (30).

Clinically, newly diagnosed type 1 diabetes patients have higher GFRs than non-diabetic individuals of the same age. Furthermore, the GFR can rise to 160–180 ml/min in around 25–40% of individuals with type 1 diabetes. This elevation in GFR is assumed to be related to metabolic control, and GFR returns to normal as blood glucose becomes normal by insulin therapy (31).

In type one DM, uncontrolled hyperglycemia is the most crucial cause of hyperfiltration. However, studies have shown that not all cases of hyperfiltration are related to glycemic

control. Initial hyperfiltration that occurs before insulin therapy or during the early stages (first few months) of type 1 DM can be reversed by insulin treatment (32). In contrast, late-onset or persistent hyperfiltration can persist for extended periods (several years). It may not be associated with glycemic control, as assessed by glycated hemoglobin (HbA1c) measurements years after diabetes onset. This may be due to the biphasic relationship between plasma glucose and glomerular filtration rate (33).

Anomalies in the glomerulus and glomerular arteries result in glomerular hyperfiltration. The transmembrane hydraulic pressure gradients, the ultrafiltration coefficient, and the kidney's plasma flow are some variables that affect the glomerular filtration rate (34). The differences in renal arteriolar resistance between afferent and efferent kidney arterioles determine the renal plasma flow. The difference in mean pressure between the proximal tubule and the glomerular capillary represents the transmembrane hydraulic pressure gradient. At the same time, the ultrafiltration coefficient is connected to the permeability and surface area of filtration. All of these characteristics are at altered levels in patients with diabetes mellitus, while it's yet unknown when these dynamic changes occur (35).

Hyperfiltration is also a result of multifactorial intraglomerular hypertension. Coexisting systemic hypertension in many diabetes individuals causes higher intrabdominal pressure because of obesity, and elevated glomerular osmotic pressures ultimately contribute to this (36).

Hyperglycemia causes hyperfiltration by Sodium-glucose Cotransporter-2 (SGLT2)-mediated proximal tubular sodium reabsorption and subsequent inhibition of tubuloglomerular feedback (TGF), recent experimental evidence suggests that Sodium-glucose Cotransporter-1 (SGLT1) activation at the macula densa cause glucose-induced hyperfiltration in isolated nephrons. We hypothesize that when the nephron number is critically reduced, it leads to decreased sodium delivery to the macula densa by increased SGLT2 activation and increased glucose at the macula densa both inhibit TGF and exacerbate glomerular hyperfiltration in chronic kidney disease (37).

3.1. Hemodynamic Effects and Endothelial Injury

The proper functioning of nephrons relies heavily on maintaining hemodynamic equilibrium, which revolves around the RAAS. Renin, produced by juxtaglomerular cells near the afferent arterioles, is a vital enzyme in activating this system. Angiotensin II, produced by the activation of renin-angiotensin- system (RAS), binds strongly to two specific receptors: angiotensin type 1 (AT1) and angiotensin type 2 (AT2). These receptors have diverse effects (38), with AT1 increasing resistance in the efferent arterioles to maintain intraglomerular pressure and renal filtration rate. At the same time, AT2 modulates prostaglandin release in the kidneys to counteract the effects of AT1 on blood pressure (39). Elevated levels of angiotensin II also have nonhemodynamic effects, such as increasing aldosterone production from the adrenal glands, inducing fibrogenic chemokines (monocyte chemoattractant protein 1[MCP-1] and transforming growth factor β [TGF-β]), and activating macrophages, all of which contribute to the inflammatory processes leading to renal injury (40).

Transforming growth factor β (TGF-β), a well-researched growth factor has been heavily implicated in developing diabetic kidney disease (DKD). In studies with diabetic subjects, the

introduction of TGF-β neutralizing antibodies resulted in a decrease in kidney enlargement and maintained kidney function (41). Interestingly, reduction of albuminuria, a key marker of DKD, was not observed using TGF-β neutralizing antibodies (42). Additionally, a trial involving 77 individuals diagnosed with diabetic nephropathy found that treatment with pirfenidone, a TGF-β production inhibitor, did not decrease urine TGF-β levels (43).

3.2. Metabolic Changes

When a person has diabetes, their body's metabolic pathways become imbalanced. This can lead to high levels of sugar in the blood, which activates several pathways such as Rho-associated protein kinase (RHO/ROCK), pylol, hexosamine, advanced glycation end products (AGEs), and protein kinase C (PKC). These pathways produce a high amount of reactive oxygen species (ROS) and increase levels of mitogen-activated protein kinase (MAPK), Janus kinase (JAK) signal transducers and activators of transcription, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) (44), which all play a role in creating inflammation and fibrosis. MAPK is also linked to the production of extracellular matrix and damage to podocytes (45). NFκB signals the creation of cytokines and adhesion molecules, including macrophage chemoattractant protein (MCP-1), Interleukin 6 (IL-6), and tissue necrosis factor α (TNF-α) (46). Moreover, reactive oxygen species (ROS) can directly harm cellular structures by oxidizing various lipids, proteins, and nucleic acids. This damage is further exacerbated in cases of obesity and Type 2 diabetes, where there is a higher load of lipids (47).

3.3. Inflammatory Reactions

When blood sugar levels rise to a dangerous level, cells can become damaged. This triggers the release of proinflammatory compounds, including TNF-α and interleukin 1 (IL1), as well as chemokines, adhesion molecules, and damage-associated molecular patterns (48). In response, inflammatory cells such as macrophages, monocytes, T lymphocytes, and nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 protein (Nlrp-3) inflammasomes are called to the kidneys (49). The accumulation of macrophages in the glomerulus produces destructive substances such as cytokines, ROS, and proteases. This damages the kidneys and leads to fibrosis, resulting in DKD progression (50). Inflammation can lead to a buildup of neutrophils, macrophages, oxidized lipoproteins, and immune complexes (28). This ongoing process can also increase the production and deposition of amyloid A protein, which can help track disease progression (51). The MCP-1 signaling pathway can disrupt the structure of the actin cytoskeleton and the stability of nephrin, leading to damage to podocytes. High glucose levels can promote the production of adhesion molecules in cells and cause abnormalities in tight junctions, ultimately resulting in proteinuria (52).

In studies on mice with both types 1 and 2 diabetes, it was found that removing MCP-1 and intercellular adhesion molecule 1 (ICAM-1), responsible for attracting macrophages to the kidneys, was linked to lower levels of albuminuria and inflammation (53).

3.4. Oxidoreductive Stress

The development of diabetic microvascular problems, including nephropathy, is acknowledged to be primarily influenced by hyperglycemia (54). Higher glucose concentrations have been demonstrated to affect cytokine production, which may affect the in vitro proliferation of renal cells (glomerular mesangial cells and proximal tubular epithelial cells) (55). Precise techniques for creating cellular models of diabetic nephropathy and researching their metabolism were developed based on this (56).

Hyperglycemia is known to cause increased production of superoxide (O2−) from various sources, such as mitochondria, NADPH oxidase, and uncoupled nitric oxide synthase (NOS). Nitric oxide and O2− may then react, removing or lessening the protective effects of NO on the vascular system and producing peroxynitrite in the process (57).

In addition, chronic hyperglycemia triggers the polyol pathway, Advanced glycation end products (AGEs) synthesis, and Protein kinase C (PKC) activation, all of which raise reactive oxygen species ROS and oxidative stress levels (58).

Damage to vital cellular components and DNA results from elevated kidney ROS levels (59).

3.5. Genetic Modification

Patients with diabetes have aging effects and DNA damage due to hyperglycemia, which damages chromosomal telomeres shortening,35 which causes DKD and proteinuria advancement (60). DNA damage triggers several kinases, such as the mutant ataxia-telangiectasia kinase and Rad3-related, after which p51 and p21 are activated. Cyclin-dependent kinase is inhibited by this, preventing retinoblastoma from being phosphorylated protein, which is necessary for transcription of E_2F transcription of DNA mediated by a factor—this reluctance of the transcription factor E_2F results in irreversible termination of the cell cycle (61).

DNA methylation is a process carried out by specific enzymes called DNA methyltransferases (DNMTs), which transfer a methyl group to the 5' end of a particular part of the DNA called cytosine guanine (CpG). Among these enzymes, DNMT1 is involved in DNA replication, while DNMT3a and DNMT3b work to re-methylate DNA during cell development. This methylation can directly hinder the binding of the transcription complex in the gene's promoter region or indirectly recognize the presence of 5-methylcytosine through a methyl-binding protein, which recruits co-repressors to bind to the promoter region (62). As a result, disruptions in transcription can cause abnormal methylation of crucial genes, potentially leading to diseases (63).

Histone Modification: - In eukaryotic cells, histones are highly conserved proteins that can bind to DNA to create nucleosomes, which are the fundamental building blocks of chromatin structure. Numerous specialized enzymes may modify histones, including methylation, acetylation, phosphorylation, and ubiquitination (64). Histone methylation, demethylation, acetylation-deacetylation, and lactylation have all been extensively studied. (65).

Noncoding RNA: - Recent studies have demonstrated the significance of noncoding RNAs (ncRNAs) in developing kidney disorders and their potential application as novel biomarkers and therapeutic targets. ncRNA, or long noncoding RNA, is the most common kind of miRNA and is defined as RNA that does not code for any protein. They regulate gene expression by controlling protein synthesis at post-transcriptional and translational levels (66).

4. Structural Changes in Diabetic Nephropathy

4.1 Podocyte Injury

Podocytes are specialized cells essential for maintaining the integrity and function of the glomerular filtration barrier, which is necessary for kidney function. However, several diabetes-related factors can damage podocytes, resulting in loss of podocyte foot processes, decreased podocyte density, and even podocyte detachment or death (67). Podocyte injury is a crucial mechanism leading to proteinuria in DN, and strategies to attenuate podocyte dysregulation have emerged as potential therapeutic approaches for DN (68).

In diabetic kidney disease, podocyte damage is the first sign of glomerular injury. Podocyte enlargement and cytoskeleton rearrangement are the main characteristics of this damage, according to scanning electron microscopy (69). Podocyte damage is caused by several factors, such as lipotoxicity, hemodynamic abnormalities, oxidative stress, autophagy and mitochondrial processes malfunction, and long noncoding RNAs (lncRNAs) (70).

Damage to the podocytes, which causes proteinuria and, eventually, glomerulosclerosis, is a crucial step in the pathophysiology of DKD. Impaired autophagy is a key factor contributing to podocyte destruction in DKD. Cells use the process of autophagy extensively at times of cellular stress for energy generation and preservation of cellular homeostasis (71).

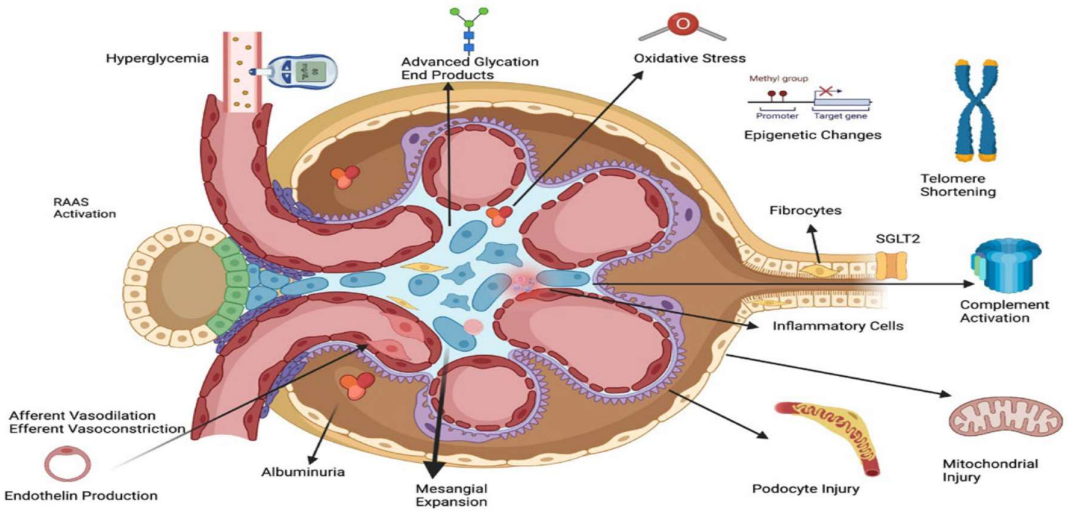
The calcium-dependent cysteine proteases calpains and the calcium (Ca 2+)-permeable ion channel transient receptor potential channel C6 (TRPC6) are two proteins that significantly hinder podocyte autophagy during DKD. In DKD, TRPC6 expression and activity are elevated, and in animal models, TRPC6 ablation guards against microvascular renal consequences of diabetes. Additionally, podocyte autophagy is inhibited by TRPC6-mediated calcium influx (72).

The pathogenic process of DN is caused by an interplay between inflammation and oxidative stress, which changes the kidney's structure and function. Podocyte hypertrophy and decreased levels of podocyte-related proteins, such as nephrin and podocin, are observed in podocytes that have lost or fused their foot processes (FP) (73).

4.2. Cellular and Mitochondrial Injury

Due to their high metabolic demands, the renal tubules contain many mitochondria. Mitochondria-related abnormalities such as mitochondrial fragmentation, reduced adenosine triphosphate, increased mitochondrial permeability, and mitochondrial uncoupling have been observed as early as four weeks after hyperglycemia in diabetic patients. One of the most important regulators of mitochondrial production is the peroxisome proliferator-activated receptor gamma coactivator-1α, whose expression is altered in DKD (74).

Figure 1 depicts some of the alterations in diabetes in the glomerulus and tubular cells (11).



5. Treatment Pharmacodynamic Pathways of Diabetic Nephropathy

5.1. Blockage of the Renin-angiotensin-aldosterone System

As mentioned above, renal inflammation is facilitated by the activation of the RAAS, which is known to convert angiotensin I to angiotensin II through an angiotensin-converting enzyme (ACE). Thus, in DN patients, RAAS inhibition with inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) have no protective benefits (75).

5.2. Sodium-glucose Cotransporter-2 Inhibitors

Sodium-glucose Cotransporter-2 (SGLT2) has a wide range of effects on the renal proximal tubule on energy metabolism, obesity, and blood glucose homeostasis. According to preliminary research, SGLT2 inhibitors vastly increase urine sugar excretion, which helps with glycemic management in type 2 diabetes (76).

5.3.3. Endothelin Antagonists

The endogenous vasoconstrictor endothelin was identified in 1988. It comprises three structurally related peptides, endothelin-1, 2, and 3. These peptides are implicated in different vasoconstrictor pathways (77). There is proof that individuals with diabetes have an overexpression of it. It has been demonstrated that endothelin receptor antagonists decrease urine protein and enhance renal microcirculation. Numerous clinical studies have been conducted to confirm the effectiveness of endothelin receptor antagonists in treating individuals with DN based on the symptoms mentioned above (78).

5.4. Glucagon-Like Peptide-1 Inhibitors

Intestinal Enteroendocrine cells (L cells) release the incretin hormone Glucagon-Like Peptide-1 (GLP-1), which stimulates pancreatic islet cell insulin production and suppresses glucagon secretion, both of which reduce blood sugar levels (79). There are several GLP-1 receptors in many different organs, such as the stomach, lungs, and kidneys. Moreover, GLP-1 activation prevents proteinuria, oxidative stress, and angiotensin II-mediated inflammation. GLP-1 agonists offer DN patients a novel and potentially beneficial treatment alternative because of these results (80).

5.5. Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) Inhibitors

A transcription factor called NFκB controls the expression of genes that code for cytokines, cell adhesion molecules, growth factors, and specific proteins during the acute phase. Numerous substances, including cytokines, ROS, inhaled particles, UV radiation, and pathogens, can activate NFκB through conventional or alternative signaling pathways (81). While total, ongoing suppression of NFκB may result in death, altered immune cell formation, and delayed cell proliferation, inflammation causes inappropriate activation of NF-kB. Thus, the potential benefit of using NFκB modulator techniques for treating numerous disorders, including DN, seems inevitable (82).

5.6. Antioxidants

Reactive oxygen species and oxidative stress are well known for their detrimental effects on all body functions. Within DN, it has been demonstrated that some antioxidants slow through the procedure. Supplements containing vitamin E, pyridoxamine, and motor (in mice) have been studied (83).

6. Conclusion and Recommendation

The primary pathophysiological criteria of diabetic nephropathy are due to several factors, including enhanced glomerular filtration (hyperfiltration) caused by multifactorial origin mainly due to high osmolarity that is induced by hyperglycemia, hemodynamic effects, and endothelial injury due to the role of TGF-β and alteration in RAAS equilibrium, metabolic changes due to several pathological pathways, inflammatory reactions that are caused by several inflammatory cells and inflammatory mediators, oxidoreductive stress that is caused by several reactive oxygen species and free radicals that are induced by hyperglycemia, and finally genetic modifications causes such as DNA methylation, histone Modification, and noncoding RNA. There are different treatment strategies for DN, such as Blockage of the renin-angiotensin-aldosterone system, inhibition of sodium-glucose cotransporter-2, endothelin antagonism, inhibition of glucagon-like peptide-1, inhibition of nuclear factor kappa-light-chain-enhancer of activated b cells (NFκB) and the use of antioxidants.

Further studies are recommended, including more details about the ultra-structural alterations in diabetic nephropathy and clinical trials for new treatment strategies for diabetic nephropathy.

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