Potential Renal Effects of Cigarette Smoking in the Diabetic State-A review

Swarup Kumar Kundu¹a*, Badhan Roy Tanny²b

¹Department of Anatomy and Histology, Faculty of Veterinary, Animal and Biomedical Sciences, Khulna Agricultural University, Khulna-9202, Bangladesh
²Department of Gynecology and Obstetrics, Ad-din Akij Medical College and Hospital, Khulna, Bangladesh

*Corresponding author

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Abstract

Diabetes is an alarming global systemic metabolic disorder that can pose a major threat to patients. The serious consequences of cigarette smoking on the diabetic kidney are not well known among people in different countries. According to different studies, smoking enhances albuminuria in diabetic patients. On the other hand, urinary albumin is a sensitive indicator of glomerular injury. The abnormal trans-glomerular passage of albumin may be seen due to increased permeability of the glomerular capillary wall and their subsequent impaired reabsorption by the epithelial cells of the proximal tubule. Smoking with hyperglycemia increases lipid accumulation and oxidative stress, which mainly up-regulates TGF-β, accumulates AGEs, reduces nitric oxide production, and eventually causes glomerular basement membrane thickening and mesangial expansion that results in the development of glomerulosclerosis and nephropathy. The complex interaction between cigarette smoking and diabetic mellitus poses multiple challenges for researchers, physicians, and patients. Therefore, the present review article aims to find out the feasible consequences for the kidney of a diabetic patient due to the habit of cigarette smoking which may be useful for academicians and researchers in the future.

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Introduction

Diabetic nephropathy (DN) is a microvascular complication with a high level of albuminuria that is mostly recorded in the Asia Pacific region in diabetic patients (Schena and Gesualdo, 2005). According to the International Diabetes Federation (IDF) survey in 2022, one in ten adults worldwide is currently living with diabetes, and the total number is estimated at 537 million people (WDD, 2022). Diabetic nephropathy has been also reported in about 20-25% of type 1 or type II diabetes patients which may increase by 6% of people per year (Kim et al., 2001). The pathophysiological mechanisms of cigarette smoking-induced changes in renal architecture in diabetic conditions have already been noted to be complex. Podocytes are specialized epithelial cells that surround the glomerular capillaries. Podocytes act as a filtration barrier attaching with endothelial cells of the glomerular capillary loop and the glomerular basement membrane and also give support to the structure and function of the glomerulus. Reduction of podocytes causes scarring, persistent proteinuria, and finally chronic kidney disease (CKD) progression. Smoking plays an important role in the progression of proteinuria and cellular alteration in the diabetic kidney, where early podocyte loss is reported as the major cause of promoting DN progression (Jaimes et al., 2021). On the other hand, cigarette smoking causes vascular pathology and its long-term association can lead to hypertension (Salvatore et al., 2015). Smoking increases blood volume and blood pressure which finally enhances the glomerular filtration rate (GFR) though there are many controversial statements regarding this (Yoon et al., 2009). Pathological confirmation like glomerular basement membrane (GBM) thickening, tubular basement membrane (TBM) parallel thickening, and major mesangial proliferation, etc. ensure the actual state of diabetic nephropathy (Fioretto and Mauer, 2007). However, the present study aimed to focus on the renal complications due to cigarette smoking in diabetic conditions.

Diabetes and its Mechanism

Diabetes is characterized by chronic hyperglycemia, and impaired carbohydrate, protein, and lipid metabolism due to insufficient insulin secretion which has become an alarming public health issue. There are two types of diabetes mellitus (DM) such as insulin-dependent diabetes mellitus (type 1 diabetes mellitus T1DM) and non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus T2DM). T2DM is the most common form of diabetes (Yacoub et al., 2010). In Diabetes mellitus (DM), the body
cannot regulate glucose in the blood. People eat foods that are converted into glucose by the liver. This glucose provides energy to the body. Especially blood glucose is regulated by hormones secreted from β-cells of the pancreas. Pancreas also secrete some enzyme that helps to digest food and insulin allows the glucose to move from the blood into cell throughout the body. By which the blood glucose is maintained. The pancreas is unable to produce enough insulin in type 1 diabetes, and cannot transport glucose into the cells to produce energy. For this reason, animals or people may go to unconsciousness or coma situations even this condition may turn to death. On the other hand, T2DM is a complex endocrine or metabolic disorder. Obesity is the main cause of producing insulin resistance and glucose intolerance. Finally, hyperglycemia and hyperlipidemia appear and are converted into a severe threat to the body (Sugiyama, 2011).

Associated risk factors of diabetes

Insulin is the key hormone produced by the β-cells of the pancreas that helps to transport glucose from the bloodstream into the body's cells. Several associating factors for the formation of diabetes mellitus (DM) are stated below:

- Cow milk consumption may increase the risk of type 1 diabetes.
- Hypertension, polycystic ovarian syndrome, hyperlipidemia, asthma, and sleeping disorders are associated with type 2 diabetes.
- Various medications including diuretics, immunosuppressants, some antidepressants, and chemotherapy drugs can increase the risk of developing secondary diabetes.
- Radiation therapy and pancreatectomy are also risk factors for diabetes.
- Using certain agricultural pesticides during pregnancy can lead to gestational diabetes.
- Free radicals, air pollution, and cold weather can destroy insulin-producing cells and contribute to the development of various types of diabetes.
- Cigarette smoking and alcohol consumption may also destroy the insulin-producing cells of the pancreas (Moussa, 2008 and Salvatore, 2005)

Risk factors for developing diabetic renal complications

- Long-term diabetes
- Cigarette smoking in diabetic condition
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Presence of other microvascular complications
- Family history of hypertension (Ayodele et al., 2004)

How does smoking affect kidneys?

Smoking has some baleful effects on kidney functions. Blood flow disruption in the kidneys is the most common problem created by smoking. The possible way to deteriorate kidney function is given below:

Kidney structure is surrounded by many significant vascular systems. In diabetes, the small blood vessels become stiffened and gradually increase the blood pressure. In this stage, continuous smoking also increases blood pressure (BP) and may weaken or narrow the blood vessels, as a result, damaged renal arteries reduce the ability to filter blood. In turn, a damaged kidney cannot regulate blood pressure which is generally called ischemic nephropathy (Virdis et al., 2010). This high BP occurs due to peripheral vascular resistance and it gradually increases the cardiac output. This is the normal phenomenon of increasing blood pressure due to smoking in diabetes by damaging renal arteries. On the other hand, from an in vitro study, the nicotine present in the cigarette increases the level of mesangial cell proliferation and fibronectin production which plays a vital role in CKD. Endothelial cell dysfunction, and activation of growth factors (angiotensin II, endothelin-I, and TGF-β1), can also be seen due to smoking which enhances oxidative stress (Dasgupta and Chellappan, 2006). Mesangial cell proliferation mainly increases the production of TGF-β1, the major player in the genesis of renal fibrosis (Mur et al., 2004). According to studies from Egypt, cigarette smoking enormously accumulates cadmium (Cd) and lead (Pb) in the kidney tissue which may also affect the tubular cells. Whereas dietary exposure plus cigarette smoking are associated with tubular and glomerular dysfunction (EL et al., 2003).

Figure 1. Possible mechanism of kidney disease by cigarette smoking (Schena and Gesualdo, 2005)
Association between cigarette smoking and diabetic nephropathy

People affected with diabetes and high blood pressure are at risk of having heart attack or stroke. Several studies revealed that diabetic people with high blood pressure may have a chance of getting chronic kidney disease (CKD). Mainly, patients with diabetes mellitus have increased peripheral arterial resistance due to excess body fluid volume (Van Laecke and Van Biesen, 2017). According to the Multiple Risk Factor Intervention Trial (MRFIT), there is a cyclic relationship between CKD and hypertension (HTN). The elevated blood pressure gradually constricts and narrows the arteries, which finally damages and weakens throughout the body including in the kidney, and thus hampers to delivery of enough blood in the renal tissue. Long-term, uncontrolled, high blood pressure (BP) leads to high intraglomerular pressure, impairing glomerular filtration (Buffet and Ricchetti, 2012). Damage to the glomeruli leads to increased protein filtration, resulting in an abnormally high amount of protein in the urine (albuminuria or proteinuria). Albuminuria is the indicative first sign of CKD (Buffet and Ricchetti, 2012). According to the American Diabetes Association, the nicotine present in smoking suppresses appetite and increases the resting metabolic rate by which subsequent weight loss may occur. On the other hand, tobacco smoking triggers a free radical process that interferes with the functioning of vascular endothelium, increases oxidative stress, and directly damages the β-cell function (Gordon and Flanagan, 2016). Neuronal nicotinic acetylcholine receptors (nAChRs) are found in β-cell of pancreatic islets. According to several studies, there is a toxic influence of nicotine on insulin-secreting β cells. Because nicotine affects the development of pancreatic cells and increases the apoptosis of islet of β cells and finally contribute to the progression of diabetes (Bruin et al., 2010). That’s why diabetes-affected people who smoke often need larger doses of insulin to keep their blood sugar close to the target levels. Furthermore, nicotine is an active compound in cigarettes that promotes excessive oxidative stress and leads to vascular endothelial cell dysfunction (VED). Eventually, nicotine also up-regulates the expression of transforming growth factor-β (TGF-β) which is the main risk factor involved in causing diabetic nephropathy (Forbes et al., 2008).

Role of macrophages (M1/M2) in the progression of diabetic kidney disease

Diabetic nephropathy is a condition of end-stage renal disease. Resident macrophages may activate by the accumulation of glucose and metabolites which have a role in the development of renal disease (Collins et al., 2015). The M1 macrophages involved in the inflammatory response secrete pro-inflammatory cytokines like CD68+/iNOS+, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-12, and IL-23 and M2 macrophages involved in anti-inflammatory response by secreting anti-inflammatory cytokine-like CD68+/Arg-1+ and transforming growth factor-β (TGF-β) (Ma et al., 2022). Though M1 and M2 play the opposite role in renal inflammation. At the early stage of renal injury, macrophages are activated by pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), interferon-gamma (IFN-γ) and M1 macrophages have inflammatory effects with high expression of pro-inflammatory mediators like inducible nitric oxide synthase (iNOS) and promote tissue inflammation and damage. M2 macrophages have immunomodulatory, pro-fibrotic, and repairing effects with high expression of CD206, CD163, and arginase-1 (Arg-1). Alternatively, M2 macrophages secrete anti-inflammatory (IL-10) and pro-fibrotic cytokines (TGF-β) that promote tissue repair and fibrosis. High expression of TGF-β activates mesangial cells to produce extracellular matrix deposition via TGF-β1/Smad3 signaling pathway (Zhu et al., 2019). On the other hand, podocytes are the important parenchymal cells of the kidney, and M1 macrophages promote podocyte apoptosis by secreting the TNF-α (Lee et al., 2011).

Histopathological alteration of kidney in diabetic nephropathy condition

Glomerular changes are the most common characteristics in DN conditions. Diabetic patients with the habit of cigarette smoking, develop elevated serum creatinine levels as well as occur glomerulonephritis. Smoking can seriously affect the renal tissue, damage the vascular system as well as effects cardiovascular function. The most common pathological changes of diabetic nephropathy are the glomerular basement membrane thickening (Pourghasem et al., 2015) nodular sclerosis, (Markowitz et al., 2015) mesangial expansion, glomerular sclerosis, arteriosclerosis, (Pourghasem et al., 2015) hyalinos of kidney blood vessels, tubular interstitial fibrosis (Pourghasem et al., 2015 and Vujčić et al., 2012). Stimulation of resident renal cells that produce the transforming growth factor TGF-β1 and upregulate GLUT-1 induce intracellular glucose transport, and TGF-β1 initiates extracellular matrix protein deposition (collagen types I, IV, V, and VI; fibronectin, and laminin) at the glomerular layer, thus causing mesangial expansion and thickening of the glomerular basement membrane. Mesangial cell expansion collapses the lumen of the capillaries that increases the glomerular volume (Salvatore et al., 2015; Schena and Gesualdo, 2015) and Lipofuscin storage (Pourghasem et al., 2015) in diabetic nephropathy due to changes in plasma lipoproteins, as it cannot be digested by tubular lysosomal enzymes and is eventually seen as storage as a residual body. Several studies described that protein glycosylation is the main reason for diabetic nephropathy. On the other hand, tubular hypertrophy and interstitial inflammation with mononuclear cell infiltration are indicative of histological alterations in the diabetic kidney. Such Progression of tubulointerstitial abnormalities finally leads to tubulointerstitial fibrosis and tubular atrophy (An et al., 2015). Moreover, nicotine in cigarettes possesses a toxic effect on podocytes that play a vital role in the kidney filtering function. Podocytes filter plasma proteins from leaking into the urine and are crucial for the healthy functioning of the kidneys. The loss of too many podocytes is the major risk factor for diabetic nephropathy and renal failure. According to the findings of different researchers
from both human podocytes and diabetic nephropathy in mouse models, large expression of the inflammatory enzyme COX2 and signs of oxidative stress are contributing to cellular injury. Nicotine also increases cell death and decreases the levels of synaptotigin, a protein that helps to prevent podocyte damage or death (Shafi et al., 2022).

**Conclusion**

Diabetes is now a well-known condition that is generally found in every family member who is not careful about their daily lifestyle. Several complications can arise as life-threatening problems. According to the literature, smoking undoubtedly causes various complications, especially kidney disease. From the present study, it is believed that cellular changes specifically albuminuria and macrophages (M1/M2) are the hallmarks of the progression of diabetic renal complications. Therefore, several clinical studies in model diabetic mice are needed to illustrate the pathophysiological mechanisms of cigarette smoking in producing kidney complications.

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