



Smoking and its Role in the Occurrence of Diabetes Mellitus and its Complications

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Absrtact

Diabetes is one of the most prevalent metabolic diseases that develops as a result of a combination of lifestyle, environmental, and genetic factors. Diabetes is a long-term illness marked by high blood sugar levels due to absolute or relative insulin deficiency or on by deficiencies in either the action or secretion of insulin, or both. Over 460 million persons worldwide suffer from diabetes, making it a global epidemic. Smoking is a well-established risk factor for a variety of chronic diseases, including diabetes and its associated complications. Smoking significantly increases the risk and severity of both micro vascular and macro vascular complications in people with diabetes. These complications include retinopathy, nephropathy, neuropathy, cardiovascular diseases (CVD), and an increased risk of infections. Smoking exacerbates the pathophysiological processes that contribute to the development and progression of these complications, especially through mechanisms such as increased oxidative stress, inflammation, endothelial dysfunction, and impaired wound healing. Insulin Resistance is a key factor in the development of Type 2 diabetes and is also implicated in a range of other metabolic disorders, including obesity, hypertension, and dyslipidemia. Insulin resistance typically arises due to genetic factors, poor diet, physical inactivity, and obesity, but emerging research has shown that smoking is also a significant contributor to its onset and progression of diabetes. This article shows the relationship between smoking and diabetes, examining how smoking contributes to the onset, progression and complications of diabetes. The review highlights the adverse effects of smoking on insulin sensitivity, glucose metabolism, and the development of chronic complications of diabetes. In addition, the article emphasizes the significance of smoking cessation as a key strategy in reducing the risk of diabetic complications and improving patient outcomes. Ultimately, this article aims to raise awareness about the detrimental role of smoking in diabetes care and stress the importance of public health initiatives focused on both diabetes prevention and smoking cessation.

Keywords: Complications, Diabetes, Insulin resistance, Smoking

Introduction

One of the modifiable risk factors for a number of chronic illnesses, including diabetes, cancer, asthma, chronic obstructive lung disease, and cardiovascular disease (CVD), is smoking. One of the few interventions that can be advised for people with diabetes in a safe and economical manner is quitting smoking. According to the American Diabetes Association's guidelines, quitting smoking is one of the most crucial things you can do to avoid developing problems from diabetes [1].

Chronic hyperglycemia is the primary symptom of diabetes mellitus, a metabolic regulatory failure. Insulin resistance, decreased insulin production, or both could be the main reasons. Additionally, diabetes may arise



directly as a result of other illnesses, such as exocrine pancreatic disorders, Gestational Diabetes and others [2]. Diabetes type 1 and type 2 are diverse conditions with widely differing clinical manifestations and course of the disease. At the time of diagnosis, some people cannot be categorically identified as having type 1 or type 2 diabetes, although classification is crucial for therapeutic decisions. The conventional beliefs that type 1 diabetes exclusively affects children and type 2 diabetes only affects adults are no longer true, since both illnesses affect people of all ages. About half of children with type 1 diabetes have diabetic ketoacidosis (DKA), and they frequently exhibit the classic signs of polyuria and polydipsia [3].

Glucose intolerance, metabolic syndrome, and insulin resistance are thought to be disorders with a shared history and close connections. Particularly in the pathophysiology of type 2 diabetes, which manifests years before overt hyperglycemia, rising insulin resistance appears to be the main contributing cause [4].

A higher risk of cardiovascular events and death is linked to smoking. Smoking raised the risk of myocardial infarction, stroke, and coronary heart disease (CHD) by [5]. There is a direct correlation between daily cigarette smoking and the risk of CHD, stroke, and proteinuria. Smoking is a significant modifiable risk factor in the development of type 2 diabetes and its associated complications. The toxic chemicals in cigarettes disrupt insulin function, promote inflammation, and worsen other metabolic factors, all of which contribute to the onset and progression of diabetes. Furthermore, smoking accelerates the complications of diabetes, including cardiovascular diseases, kidney failure, neuropathy, and retinopathy. One of the main risk factors for cardiovascular disease (CDV), which significantly increases the burden of cardiovascular disease overall, is smoking. As a result, smoking raises the risk of macro vascular problems in DM patients [6].

Article aims to raise awareness about the detrimental role of smoking in diabetes care and stress the importance of public health initiatives focused on both diabetes prevention and smoking cessation. Therefore, smoking cessation is essential for preventing diabetes and managing its complications, making it a critical component of any diabetes care plan. Public health campaigns and healthcare providers must emphasize the importance of quitting smoking for individuals with diabetes or those at risk, as the benefits of smoking cessation can have a profound impact on long-term health outcomes. Smoking cessation plays an important effect on the overall health of a person. It can prevent smoking related complications like cardiovascular diseases, renal diseases, and hypertension etc. Therefore, the importance of article shows the complex relations between smoking and diabetes.

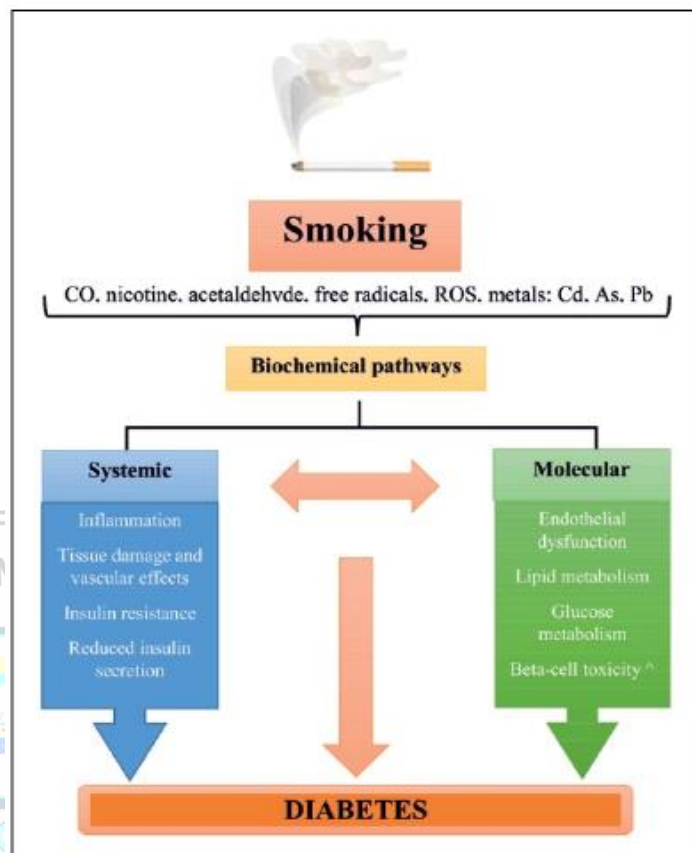
Smoking

One of the modifiable risk factors for a number of chronic illnesses, including diabetes, cancer, asthma, chronic obstructive lung disease, and cardiovascular disease (CVD), is smoking. One of the few interventions that can be advised for people with diabetes in a safe and economical manner is quitting smoking. According to the American Diabetes Association's guidelines, quitting smoking is one of the most crucial things you can do to avoid developing problems from diabetes [1].

Numerous studies have demonstrated that smoking's detrimental effects on diabetes mellitus are linked to both micro vascular disease and macro vascular problems [7, 8]. Smoking is linked to central obesity even though it is known to reduce body weight [9]. In addition to directly harming β -cell function, substances included in tobacco smoke surely because free radical activities, disrupt vascular homeostasis and the healthy operation of the vascular endothelium, and enhance inflammation and oxidative stress [10, 11].

As tobacco products like cigarettes contain 7357 chemical compounds and 10 15 to 10 17 free radicals, in addition to the well-known compounds like carbon monoxide, tar, arsenic, lead, and nicotine, this literature is extensive and complex, potentially contributing to the pathogenesis through a variety of pathways which leads to diabetes [12, 13, 14].

To complicate matters, each of these pathways is neither mutually exclusive nor linear, and there are a vast number of interactions between chemicals, and interconnectivity between the inflammatory and biochemical pathways that they induce (Figure). Many previous studies documenting the impact of smoking on health did not discuss separately the results for subgroups of patients with diabetes, suggesting an estimated risk of complications that is similar to the general population. Understanding the hazardous effects of smoking on diabetes mellitus may lead to increased emphasis on smoking prevention and smoking cessation as important strategies in the management of this condition.



Diabetes

Diabetes is a chronic condition characterized by elevated blood glucose levels due to defects in insulin secretion, insulin action, or both (American Diabetes Association [ADA]. Type 2 diabetes (T2D) is the most common form, accounting for around 90-95% of all diabetes cases. Diabetes is a global epidemic effecting over 460 million adults worldwide, and this number is expected to rise (International Diabetes Federation [IDF], 2019). The association between smoking and diabetes risk has become an increasingly important area of research, with smoking being identified as a modifiable risk factor for T2D.

The Relationship between Diabetes and Smoking

Cigarette smoking is an independent risk factor for type 2 diabetes, according to numerous epidemiological studies. Diabetes is one of the most prevalent metabolic diseases, supported by a confluence of lifestyle, environmental, and genetic factors [15, 16, 17]. The 5-year Insulin Resistance Atherosclerosis Study, which included a sample of 25% smoking and 14% non-smoking individuals with diabetes, confirmed the substantial impact of cigarette smoking on the development of diabetes in adults. The study included nearly a thousand individuals who were declared healthy and did not have diabetes.

Smokers had a statistically increased risk of type 2 diabetes than non-smokers after accounting for anthropometric, behavioral, metabolic, gender, racial, and hypertension-related variables. Additionally, smokers with normal glucose tolerance were found to have a greater chance of developing diabetes. Additionally, the length of smoking was positively correlated with the incidence of type 2 diabetes.

Hyperglycemia, hyperinsulinemia, and hypertension are more likely to occur during periods of heavy cigarette smoking [18]. Cigarette smoking is a risk factor for type 2 diabetes, according to other research. Compared to males who never smoked, men who smoke more than two packs of cigarettes a day are 45% more likely to acquire diabetes. In contrast, women who smoke more than 40 cigarettes a day are up to 75% more likely to acquire diabetes than women who do not smoke.

Within five years for women and over ten years for males, quitting smoking lowers the risk to that of non-smokers [19].

There aren't many specific researches on how smoking affects women's chance of developing diabetes. After controlling for other risk factors, the risk for diabetes in smokers was 1.42, according to the findings of the Nurses' Health Study in the United States, which included 114,247 women and 1,227,589 person-years of follow-up [20]. According to other research, smoking in the past and present is primarily linked to a higher risk of developing diabetes mellitus in males but much lower in women, and the association between smoking and fasting glucose seems to differ between the sexes [21]. After adjusting for other risk factors like alcohol use and obesity, a longitudinal study of Japanese men conducted between 1984 and 1992 found that the risk of type 2 diabetes was three times higher for those who smoked 16–25 cigarettes per day than for those who never smoked [22]. From 1994 to 1999, a follow-up analysis of this Japanese male cohort revealed that the number of years smoked and the amount of intake were positively connected with impaired fasting glucose, which frequently leads to type 2 diabetes, as well as the onset of type 2 diabetes [23]. In conclusion, the majority of research does connect diabetes with cigarette smoking in a dose-response manner. According to a meta-analysis of data from 46 studies evaluating the relationship between smoking and the incidence of type 2 diabetes, active smokers were more likely than non-smokers to get the disease.

Additionally, by classifying the respondents based on their level of smoking intensity, this meta-analysis examined the dose-response effect. The quantitative summary demonstrates that the RR of diabetes rises in a dose-dependent manner as smoking intensity (measured by the number of cigarettes smoked daily) rises [24].

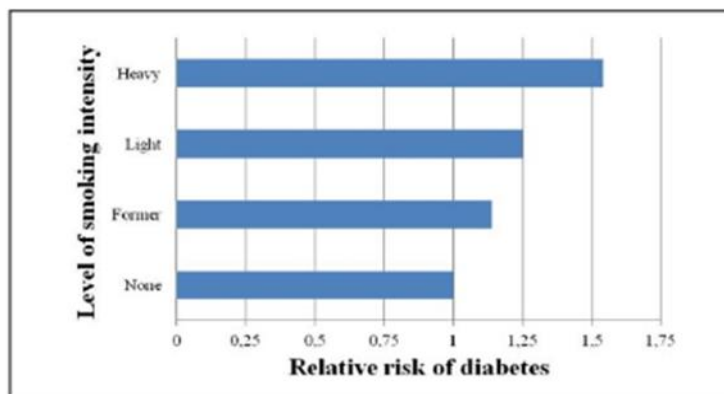


Figure 2. Pooled RR of diabetes associated with smoking intensity. Light smoking defined in most studies as current smoking of 0–19 cigarettes/day and heavy smoking defined in most studies as current smoking of 20 or more cigarettes/day.³⁸

Reduced Insulin Secretion

The β cells of the pancreatic islets were shown to contain neuronal nicotinic acetylcholine receptors (nAChRs). It was discovered that nAChR subunits, including α -2, α -3, α -4, α -5, α -7, and β -2, are present on the surface of the pancreatic islet cells. Reduced β cell insulin production was noted in both the acute (60 min) and chronic (48 h) nicotine exposure cases. The results imply that AChRs are crucial in regulating the release of hormones by β cells. Additionally, isolated human islet cells were shown to decrease insulin production when exposed to nicotine concentrations greater than 1 $\mu\text{mol/L}$ [25].

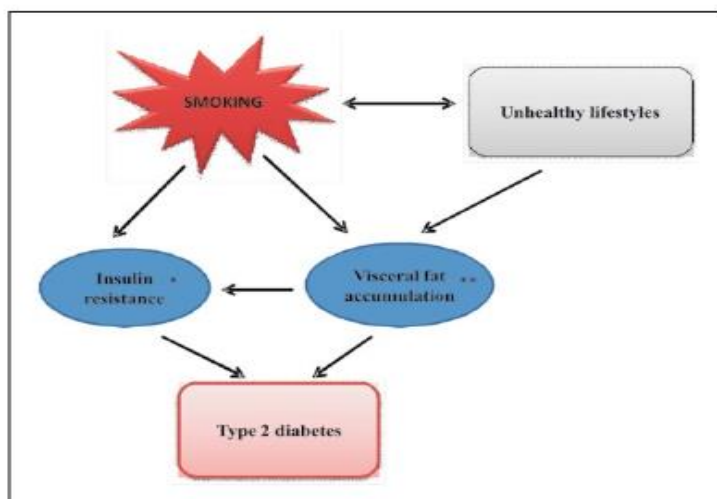
These results suggest that nicotine may, at least partially, impair pancreatic β -cell function and that functional nicotinic receptors are found in pancreatic islets and β cells. Therefore, the mechanism of nicotine's harmful

influence on insulin-secreting β cells may account for the existence of neuronal nicotinic receptors responsive to nicotine in pancreatic cells.

Numerous researches on animals have shown that nicotine may impact pancreatic cell growth and have a role in the onset of diabetes. Numerous investigations have demonstrated that in animal models exposed to nicotine, nicotine can enhance islet β cell apoptosis. The effects of prenatal and postnatal nicotine exposure on the function of the β cells of the pancreatic islets were examined in an animal model experiment. Pregnant rats used in the study received injections of a hydrogen tartrate nicotine solution, while saline was given to the control group. Nicotine and saline were administered for 21 days following delivery, or until the end of lactation. Through the mitochondrial and/or death receptor pathway, nicotine exposure has been shown to induce β -cell malfunction and increased β -cell apoptosis, which in turn can result in decreased glucose metabolism [26]. Smoking has been associated with an increase in visceral fat, which is a known risk factor for the development of insulin resistance and T2D. Visceral fat is particularly harmful due to its proximity to key organs involved in glucose metabolism, such as the liver and pancreas.

Insulin Resistance

In healthy people, glucose levels are maintained within the normal range through proper insulin secretion by β cells and the sensitivity of peripheral tissues to the action of this hormone. Insulin resistance, metabolic syndrome and glucose intolerance are regarded as disturbances with a common background and strong interrelations particularly in the pathophysiology of type 2 diabetes, which manifests years before overt hyperglycemia, rising insulin resistance appears to be the main contributing cause. The islet β cells "try" to compensate by secreting more insulin in the early stages of enhanced insulin resistance [27]. *Figure* shows relationship between smoking and Insulin Resistance. Nicotine and other chemicals in tobacco smoke have been shown to increase insulin resistance, a major factor in the pathogenesis of T2D. Nicotine stimulates the sympathetic nervous system, leading to an increase in cortisol levels, which can impair insulin sensitivity. Furthermore, exposure to tobacco smoke has been shown to disrupt glucose homeostasis, exacerbating the metabolic deregulation that leads to diabetes. The detrimental effects of cigarette smoking on peripheral insulin action, which seems to be "dose dependent," have been demonstrated in numerous investigations. Acute smoking increases insulin resistance in young, healthy males. An hour after smoking, smokers' insulin resistance index on the homeostatic model assessment was noticeably higher. Males who smoked had a 10%–40% lower insulin-mediated glucose uptake than males who did not smoke [28, 29]. Additionally, even in the absence of other variables known to affect insulin sensitivity, long-term smoking was linked to elevated plasma insulin concentrations in healthy men. Given that long-term use of nicotine gum is linked to both insulin resistance and hyperinsulinemia, nicotine may be partially to blame for the observed rise in insulin resistance among smokers. Patients with type 2 diabetes were also assessed for the impact of persistent smoking on insulin sensitivity. The findings of this study demonstrated that smoking





patients had lower peripheral glucose metabolism than non-smokers. While there was no significant difference in blood glucose levels between smokers and non-smokers, smokers had significantly higher insulin and C-peptide responses to oral glucose dosages. Therefore, it appears that long-term cigarette smoking greatly increases insulin resistance in those with type 2 diabetes, which may have consequences for how these individuals are treated. A rapid infusion of nicotine exacerbates the insulin resistance response in individuals with type 2 diabetes, according to human tests employing the glucose-clamp technique. This finding further links nicotine to the observed alterations in insulin sensitivity in smokers.

Smoking and Diabetes Complications

Smoking is linked to a higher risk of cardiovascular events and death in people with diabetes. According to a meta-analysis of prospective studies on diabetes, smoking raised the risk of myocardial infarction by 52%, coronary heart disease (CHD) by 54%, stroke by 44%, and mortality by 48%. 5. There is a direct correlation between daily cigarette smoking and the risk of CHD, stroke, and proteinuria.

Patients with diabetes who quit smoking have been shown to have a lower risk of cardiovascular events and death than those who keep smoking. Furthermore, quitting smoking typically lowers the vascular risk for people with recently diagnosed diabetes mellitus [30].

Microvascular Complications

Additionally, smoking is linked to the early onset of microvascular problems such as retinopathy, nephropathy, and neuropathy. It's interesting to note that smoking may have negative effects on renal disease that are apart from the glycemic effect. Even studies from thirty years ago also shows that smokers with diabetes had a far greater prevalence of diabetic kidney damage than diabetic nonsmokers. Compared to non-smoking patients, smokers with diabetes have a higher risk of developing micro- or macro albuminuria and low glomerular filtration rate (GFR) [31].

The most recent study demonstrates a distinct dose-response relationship between cigarette smoking and the onset of proteinuria in males with type 2 diabetes. Diabetic retinopathy (DR), a leading cause of blindness in adults, is influenced by both hyperglycemia and smoking. The risk of DR is significantly higher in smokers with diabetes compared to non-smokers. Smoking increases the risk of DR by inducing vascular damage, increasing oxidative stress, and promoting inflammatory pathways that damage the retinal microvasculature. Diabetic Nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) and is associated with poor prognosis in individuals with diabetes. Smoking has been shown to significantly increase the risk of DN, independently of glycemic control. Smokers with diabetes have a higher likelihood of developing proteinuria (excess protein in the urine) and progressing to kidney failure. Smoking exacerbates kidney injury in diabetes through increased inflammation, increased blood pressure, and enhanced oxidative stress. Nicotine and other tobacco chemicals can increase the production of pro-inflammatory cytokines, which promote glomerular fibrosis and the development of proteinuria.

Smoking and Diabetic Neuropathy

Diabetic neuropathy (DN) affects up to 50% of people with diabetes and is characterized by nerve damage, which can lead to pain, loss of sensation, and increased risk of foot ulcers. Smoking is a well-known risk factor that accelerates the development of diabetic neuropathy. Smokers with diabetes are more likely to experience worse neuropathic symptoms compared to non-smokers. Smoking contributes to the progression of neuropathy by increasing the oxidative stress in nerve tissues, reducing blood flow to peripheral nerves, and



impairing the function of endothelial cells. These effects worsen the nerve damage caused by chronic hyperglycemia. Smoking-induced inflammation and alterations in micro vascular circulation further exacerbate the peripheral neuropathy observed in diabetic patients.

Smoking and Impaired Wound Healing in Diabetes

Smoking has been shown to impair wound healing, and this effect is particularly dangerous in individuals with diabetes, who already face delayed wound healing due to poor circulation, neuropathy, and immune dysfunction. Smokers with diabetes are more likely to experience chronic wounds and infections, especially foot ulcers, which are a common and serious complication of diabetes. Smoking reduces blood flow, decreases oxygen delivery to tissues, and impairs the function of immune cells, all of which are essential for proper wound healing. Moreover, smoking increases the production of pro-inflammatory cytokines and decreases collagen synthesis, further delaying the healing process. Advanced glycation end products (AGEs) are produced in greater quantities as a result of smoking-induced oxidative stress, aggravating retinal vascular injury. Furthermore, smoking causes the basement membrane of retinal capillaries to thicken, which increases fluid leakage into the retina and causes retinal ischemia [32].

Macro Vascular Complications

The development of CVD and CHD are a major complication in type 2 diabetes, as well as clinical CVD may also precede the development of diabetes. Therefore, there is a hypothesis that the CVD and the risk of type 2 diabetes is linked with the existence of the same factors, one of which is cigarette smoking. The RR of death and myocardial infarction is increased by twofold in smokers with diabetes compared with patients who do not smoke and stopping smoking significantly reduces the risk. Smoking induces endothelial dysfunction, increases oxidative stress, and promotes inflammation, all of which contribute to atherosclerosis. In individuals with diabetes, the combination of smoking and hyperglycemia worsens endothelial injury and increases the likelihood of plaque formation. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with diabetes. Smoking is a well-established risk factor for CVD, and its effects are even more pronounced in people with diabetes. Smoking accelerates the development of atherosclerosis (hardening and narrowing of the arteries) and increases the risk of heart attack, stroke, and peripheral arterial disease (PAD) in diabetic individuals. Smokers with diabetes are at a much higher risk of coronary artery disease (CAD) compared to non-smokers with diabetes [33].

According to the World Health Organization Multi-National Study of Vascular Disease in Diabetics, smoking is substantially linked to a higher risk of coronary heart disease (CHD) but not stroke in people with type 1 and type 2 diabetes [34].

Conclusion

Smoking is a significant modifiable risk factor in the development of type 2 diabetes and its associated complications. The toxic chemicals in cigarettes disrupt insulin function, promote inflammation, and worsen other metabolic factors, all of which contribute to the onset and progression of diabetes. Furthermore, smoking accelerates the complications of diabetes, including cardiovascular diseases, kidney failure, neuropathy, and retinopathy. Therefore, smoking cessation is essential for preventing diabetes and managing its complications, making it a critical component of any diabetes care plan. Public health campaigns and healthcare providers



must emphasize the importance of quitting smoking for individuals with diabetes or those at risk, as the benefits of smoking cessation can have a profound impact on long-term health outcomes.

Suggestions

Given the substantial negative impact that smoking has on diabetes development and complications, there are several key suggestions that can help individuals manage these effects:

1. Quit Smoking to reduce Diabetes risk by seeking professional support and gradual reduction.
2. Manage Blood Sugar levels actively.
3. Adopt a healthy lifestyle by maintaining a balanced diet and exercise.
4. Increase awareness of the dangers of smoking for Diabetic by health education.

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