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Smoking and the Risk of Type 2 Diabetes

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Abstract

Despite accumulating evidence demonstrating strong epidemiological and mechanistic associations between cigarette smoking, hyperglycemia, and the development of type 2 diabetes, tobacco abuse has not been uniformly recognized as a modifiable risk factor in diabetes prevention or screening strategies. In this review, we highlight population-based studies that have linked cigarette smoking with an increased risk of type 2 diabetes and summarize clinical and preclinical studies offering insight into mechanisms through which cigarette smoking and nicotine exposure impact body composition, insulin sensitivity, and pancreatic β cell function. Key questions for future studies are identified and strategies for smoking cessation as a means to decrease diabetes risk are discussed.

Keywords

diabetes mellitus; cigarette smoking; nicotine; tobacco

Introduction

Worldwide, diabetes mellitus affects nearly 422 million individuals and is directly responsible for 1.5 million deaths while indirectly contributing to an additional 17.5 million deaths each year [1]. Type 2 diabetes (T2D) accounts for 90–95% of diabetes cases and is

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caused by insulin resistance and progressive loss of β cell function and mass. Because T2D risk is strongly linked to environmental, nutritional, and lifestyle determinants, targeting known risk factors through early lifestyle modification remains the most effective strategy for decreasing disease prevalence and mortality [1]. According to the 2014 Surgeon General's Report, smoking increases the risk of T2D by 30–40% for active smokers compared to non-smokers, suggesting that smoking cessation should be emphasized as an essential public health strategy to combat the global epidemic of diabetes [2]. The World Health Organization recognizes smoking as a preventable risk factor for T2D and endorses smoking avoidance/cessation as part of their lifestyle recommendations [3]. However, both the American Diabetes Association and the International Diabetes Foundation do not currently include smoking as a modifiable risk factor for diabetes development or consider smoking status as factor that should prompt diabetes screening [4, 5]. In this review, we highlight key population-based studies that have linked cigarette smoking with an increased risk of T2D and summarize clinical and preclinical studies that provide insight into the mechanisms through which cigarette smoking impacts metabolic health and glucose homeostasis.

Epidemiological evidence linking cigarette smoking and diabetes

A variety of epidemiological studies have demonstrated associations between cigarette smoking and the development of T2D [6–8]. The Health Professionals' Follow-Up Study analyzed data from over 40,000 American male health care professionals who were followed with biannual surveys for over six years from 1986–1992. In this study, men who smoked 25 or more cigarettes per day had a relative risk of incident diabetes of 1.94 (95% confidence interval (CI) 1.25, 3.03) compared to non-smokers [8]. Similar results have been shown in other ethnic groups, including a study of nearly 50,000 Chinese men who were followed on average for 5.4 years. In this cohort, those who smoked more than 20 cigarettes per day had an elevated hazard ratio of incident T2D of 1.25 (95% CI: 1.00, 1.56), while men with a ≥ 40 pack-year history of smoking had an elevated hazard of T2D of 1.28 (95%CI: 1.04, 1.57) [9]. In a study of U.S. postmenopausal females, those who smoked on average 16.2 cigarettes per day exhibited a 1.28-fold increased risk of new diabetes (95% CI: 1.20, 1.36). Risk was mitigated in those who stopped smoking; after 10 years of cessation, the risk of diabetes became equivalent to that of never-smokers [10]. A similar analysis was performed in a Korean cohort of 1,236,443 men and women who were aged 30–95 years at baseline and followed prospectively over 14 years. Smoking was associated with an increased risk for diabetes treatment, hospitalization, and mortality among both men and women, and risk increased in a dose-dependent manner with the number of cigarettes smoked per day. Interestingly, data from this cohort also suggested an increased risk for men compared to women [11].

Studies have also examined associations between smoking and glycemia. In a large cross-sectional study of 2704 men and 3385 women followed in the European Investigation into Cancer (EPIC-Norfolk) study, cigarette smoking was independently associated with higher hemoglobin A1c (HbA1c) concentrations, with both male and female smokers exhibiting similar changes in HbA1c values. This analysis demonstrated that HbA1C rose by 0.12% per 20 pack-years of smoking in participants of both genders [12]. Similarly, data from the

National Health and Nutrition Examination survey, which included 17,287 adults without diabetes, showed that the mean age-adjusted HbA1C was higher in patients with elevated circulating levels of the nicotine metabolite, cotinine, while smokers exhibited a 7% increase in HbA1c compared to those who had never smoked [13].

Smoking Leads to a Variety of Chemical Exposures

Cigarettes and other smoking products contain a mix of chemical additives with the potential to impact metabolic health. Nicotine is one of the major bioactive substances in cigarettes and is among the most widely consumed additive. Nicotine is an alkaloid naturally produced by the tobacco plant that binds nicotinic acetylcholine receptors, found throughout neuronal and non-neuronal or visceral organs. These receptors participate in signaling within the central and peripheral nervous system and in a number of metabolic tissues, including pancreatic islets, adipose tissue, macrophages, liver, and skeletal muscle [14–17]. Nicotine has been shown to directly alter glucose homeostasis [18], suggesting an important role for this additive in the development of T2D. Cigarette smoking also results in increased blood serum levels of heavy metals such as lead, arsenic, and cadmium [19]. However, studies of the impact of these substances on glucose homeostasis have yielded somewhat inconsistent results. For instance, exposure to low environmental levels of inorganic arsenic in 3602 Korean adults increased the prevalence of diabetes. Additionally, glucose tolerance was inversely correlated with urinary arsenic levels, suggesting a role for the heavy metal in the development of diabetes [20]. In a Bangladeshi study, the odds ratio of diabetes was 8.83 in male smokers with arsenic blood serum levels of ≥15.5 μg/L compared to male smokers with lower arsenic levels [21]. Likewise, participants from the Canadian Health Measures survey with high urinary arsenic levels (≥22.99 μg/L) showed a nearly 2-fold increased risk of T2D compared to those with urinary arsenic levels of less than 5.71 μg/L [22]. In contrast, no significant relationship was found between levels of lead, mercury, or cadmium, and diabetes or measures of β cell function in another study of Korean men and women, even when considering the sum exposure of heavy metals [23]. Likewise, only limited data could support an association between arsenic and diabetes in chronically exposed populations in Taiwan and Bangladesh [24].

Cigarette smoking impacts body weight and composition, peripheral insulin sensitivity, and pancreatic β cell function

Whereas epidemiological studies have tested associations between smoking and diabetes development, a number of studies have also investigated mechanistic underpinnings of these associations. In aggregate, data from these studies suggest that smoking is associated with deleterious changes in body composition, despite being linked to reduced body weight [25]. Individuals who smoked >20 cigarettes per day had an adjusted odds ratio for abdominal obesity of 1.93 (95% CI: 1.16 to 3.21) as compared to never-smokers [26]. Cross-sectional data from 21,828 men and women aged 45 to 79 years in the United Kingdom demonstrated that smokers had higher waist-to-hip ratios as compared to non-smokers, and this measure was directly correlated with the amount of smoking [27]. Furthermore, in a cross-sectional study of 513 Japanese men, greater lifetime smoking exhibited a significant and positive

association with higher waist-to-hip ratio and the visceral adipose to subcutaneous adipose ratio, assessed by computerized tomography (CT) scans [25]. These findings support the general notion that smoking is linked to adverse fat distribution. Interestingly, changes in body composition associated with cigarette smoking appear to be driven primarily by nicotine signaling, both centrally and peripherally [reviewed in [16]]

Consistent with these changes in body composition, smoking acutely worsened glucose tolerance and the insulin sensitivity index in twenty chronic smokers who had paired oral glucose tolerance tests performed after smoking and under control conditions [28]. In persons with established diabetes, euglycemic hyperinsulinemic clamp analyses revealed that total body glucose disposal was reduced in smokers compared to those who did not smoke [29]. In addition, data support a direct effect of nicotine on glucose homeostasis. In this regard, results from hyperglycemic-hyperinsulinemic clamp analyses performed on subjects with established T2D revealed that active smoking as well as acute transdermal nicotine patch administration led to decreased insulin action [18].

In addition to the above effects on body composition and peripheral insulin signaling, Clinical studies also suggest that smoking impairs measures of β cell function. Among 1,199 Japanese men aged 30–79, the incidence of impaired insulin secretion, as represented by a change in the insulinogenic index during a 75-gram oral glucose tolerance test over a mean follow-up of 2.8 years, was 1.06 in ex-smokers versus 1.95 in current smokers, as compared to never-smokers. Furthermore, the number of pack-years of smoking was found to dose-dependently impair β cell function [30]. Separately, Ostgren and colleagues studied nearly 260 Swedish men and found that current cigarette smokers had lower β cell function, as measured by the homeostatic model assessment method (HOMA-β), compared to never smokers (58.1 vs. 90.1; 95% CI: 17.8–43.5, $p < 0.001$). This difference remained significant even after adjustment for age, body mass index, alcohol intake, and physical activity. Interestingly, results from this study suggested dichotomous effects by gender, as no significant relationships were found between smoking and β cell function among nearly 350 female never and current smokers [31].

Molecular mechanisms underlying the development of altered glucose homeostasis in smokers

To gain insight into the effects of smoking on peripheral insulin signaling, Bergman and colleagues analyzed skeletal muscle biopsy specimens from smokers and nonsmokers and found that smokers had increased Ser636 phosphorylation of IRS-1, a known inhibitory modification with negative effects on insulin sensitivity. Smokers also exhibited decreased expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ), a transcription factor known to promote insulin sensitivity [32]. A later study from this same group characterized the *in vitro* effects of nicotine on skeletal muscle cultures and showed that nicotine exposure resulted in increased IRS-1 Ser636 phosphorylation and activation of mTOR and MAPK signaling, while rapamycin-induced inhibition of mTOR was able to reverse nicotine-induced alterations in IRS-1 signaling [33].

Nicotine has also been reported to increase lipolysis from adipose tissue [34] by activating AMP-activated protein kinase α2 (AMPKα2) in adipocytes, leading to increased phosphorylation and proteosomal degradation of MAP kinase phosphatase-1 (MKP1). Nicotine-induced reductions in MKP1 resulted in activation of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, ultimately promoting IRS-1 degradation and loss of insulin-mediated inhibition of lipolysis [35]. Consistent with these observations, serum triglyceride levels have been shown to be higher in smokers compared to nonsmokers [36]. Furthermore, cigarette smoking was independently associated with the onset of non-alcoholic fatty liver disease (NAFLD) [37]

Smoking may also impact insulin sensitivity through additional epigenetic mechanisms. Analysis of 432 blood samples from subjects in the Northern Sweden Population Health Study revealed that 95 DNA methylation sites within 66 distinct chromosomal regions were differentially methylated in smokers. Interestingly, genes associated with “insulin receptor binding” and “negative regulation of glucose import” were enriched within the dataset, suggesting that smoking-induced diabetes susceptibility may arise from aberrant methylation of DNA [38]. In support of this theory, a recent paper found that cigarette smoking is associated with altered methylation patterns in several previously identified diabetes-related genes [39]

In contrast to studies testing molecular associations between smoking and reduced insulin sensitivity, considerably less is known about how smoking impacts pancreatic β cell function. Nicotinic receptors have been reported on pre-synaptic sympathetic nerve terminals and postsynaptic receptors within islets, while nicotinic receptor agonism and antagonism have been shown to modulate insulin secretion. Stagner and Samols performed a series of experiments using an *in vitro* canine whole pancreas perifusion model. Acutely, perifusion of canine pancreas with nicotine resulted in transient stimulation of insulin secretion, which was blocked by ganglionic postsynaptic nicotinic receptor blockade using alpha-bungarotoxin. Interestingly, pre-synaptic receptor blockade also led to decreased insulin secretion [40]. However, in another study, contrasting effects were observed in isolated rat islets, where insulin secretion was increased by alpha-bungarotoxin. Moreover, nicotine suppressed alpha-bungarotoxin-induced increase in insulin secretion [41]. In yet another analysis, acute nicotine treatment also moderately decreased insulin secretion in human islets, while chronic treatment for 48 hrs led to a significant reduction in insulin secretion [42]. Some of these discrepancies may be related to species-related differences as well as differences between experiments performed using a pancreas perifusion system and isolated islets. However, available data fail to provide clarity regarding the effects of nicotine on normal pancreatic β cell function. As such, additional mechanistic studies are warranted to more completely understand the physiology of nicotinic signaling in the islet as well as the clinical association between smoking and reduced β cell function [30, 31].

Not withstanding these uncertainties, smoking and nicotine exposure may induce a pro-inflammatory metabolic state that would be expected to impact both insulin sensitivity and β cell function. Nicotine has been shown to decrease activity of free radical scavenging enzymes, in turn increasing generation of hydroxyl free radicals by increased superoxide anion and hydrogen peroxide [43]. Furthermore, skeletal muscle expression of monocyte

chemotactic protein-1 was increased in smokers compared to non-smokers [32]. In healthy middle-aged non-obese men, long-term nicotine gum chewers (NGCs) had greater plasminogen activator inhibitor-1 activity compared to non-smoking controls [36]. Smoking also causes an endogenous stress response characterized by increased circulating levels of cortisol, catecholamines, and growth hormone that can impact glucose homeostasis at both the level of the β cell function and peripheral tissues [44, 45].

Alternative smoking products and T2D risk

Of note, the increased risk for T2D development associated with tobacco use may not be limited only to cigarette smoking. There is evidence to suggest that heavy use of alternative smoking products, including smokeless tobacco (oral moist snuff, “snus”), may also impact diabetes development [46, 47]. A prospective population based study of Swedish men demonstrated an increased risk for the development of T2D in individuals who used >5 boxes of snus per week (odds ratio: 3.3, CI 1.4–8.1) [47]. In a second study, also performed in Sweden, high consumption of smokeless tobacco (“snus”) predicted an increased risk of type 2 diabetes in a 10-year prospective study of middle-aged men. In contrast, another Swedish study failed to find an association between snus use and T2D [48]. However, more recently a pooled analysis from five cohorts revealed a hazard ratio of incident type 2 diabetes of 1.15 (95% CI: 1.00–1.32) in current users of snus compared to never users. Moreover, risk increased with heavier weekly use [49]. In aggregate, these findings appear to support an increased risk of diabetes with smokeless tobacoo at least in the the Swedish population, but further studies are needed to determine how applicable these findings are to other populations and ethnic groups.

Developmental effects of smoking

Smoking during pregnancy is associated with an increased risk of gestational diabetes mellitus (adjusted odds ratio = 1.9, 95% CI: 1.0, 3.6) [50]. Moreover, the incidence of diabetes in offspring may be affected by exposure to smoke *in utero*. For example, the 1958 British Birth Cohort study measured Hb1Ac levels in participants at age 45, and observed that maternal smoking was associated with an increase in the prevalence of HbA1C >6% and development of T2D in adulthood [51]. Likewise, data from 34,453 participants in the Nurses’ Health Study II revealed that maternal (and to a lesser extent, paternal) smoking during the first trimester was an independent risk factor for the development of T2D in offspring, even after adjusting for confounders such as birth weight and later-life BMI (hazard ratio 1.34, 9% CI 1.01–1.76) [52]. Analysis from the Prospective Singleton Pregnancy Cohort showed slightly higher proinsulin-to-insulin ratios in offspring of smokers compared to nonsmokers, suggesting alterations in pancreatic β cell function and potentially increased β cell stress at birth (35). Finally, offspring of rats exposed to nicotine exhibited altered insulin biosynthesis, β cell degranulation, increased islet oxidative stress, and impaired glucose-stimulated insulin secretion, all of which were preceded by the appearance of mitochondrial structural abnormalities [53]. Furthermore, exposure to secondhand (passive) cigarette smoke after the prenatal period is also linked to an increased risk for T2D development. A recent meta-analysis of prospective studies including almost 6 million individuals reported a 22% increase in the risk for development of T2D in those never

smokers exposed to passive smoke compared to never smokers not exposed to passive smoke [54]

Smoking Cessation and Glucose Homeostasis

Active smoking has been associated with reduced appetite and weight loss. On the other hand, smoking cessation is often associated with weight gain. In some studies, cessation of cigarette smoking has also been linked to increased incidence of T2D, likely due to increased weight gain upon withdrawl of nicotine, and this increased risk of T2D was highest in the first 3 years post-cessation [55]. Previous studies have suggested significant heterogeneity in the magnitude of weight gain following smoking cessation, with the greatest weight gain often seen in individuals with the highest daily cigarette consumption [56]. Studies of gender-related differences in post-cessation weight gain (PCWG) have yielded conflicting results, with some studies showing greater weight gain in men and others showing higher weight gain in women [57, 58]. Self-report data from the NHANES study revealed an average PCWG of approximately 1.4 kg (95% CI: 0.8 to 2.0) in recent quitters who had stopped smoking within the past year. In this study, normal and overweight individuals were at greatest risk of weight gain, while obese individuals tended to lose a small but insignificant amount of weight [59]. Mean one-year weight gain in another sedentary group of smokers was documented to be between 3.3–3.9 kg [57]. While the effects of smoking cessation on glucose homeostasis may be often confounded by the presence of weight gain, at least one study has shown that prior to any change in weight, short-term smoking cessation of 1–2 weeks was sufficient to reverse defects in insulin sensitivity and skeletal muscle insulin signaling in both male and female young adults [33]. Longer term studies are needed to define how these parameters change over time.

Varenicline is a partial nicotine receptor agonist that has been shown to promote smoking cessation, with abstinence rates up to two- or three-fold higher compared with non-pharmacological means. Similarly, buproprion, an anti-depressant, and nicotine replacement therapy via a patch or gum have been shown to be more efficacious in promoting abstinence compared to placebo treatment [60]. A Cochrane systematic review suggested that personalized weight support and counseling may successfully reduce post-cessation weight gain. Buproprion, varenicline, and nicotine replacement therapy have also been shown attenuate weight gain acutely during active treatment; yet it is unclear whether such therapies can help control weight in the long term [61]. Moreover, given studies suggesting an independent effect of nicotine to perturb glucose homeostasis, it remains to be clarified whether cessation strategies that include nicotine agonists differentially impact long-term changes in glucose homeostasis. Interestingly, *in vitro* treatment of INS-1 β cells with nicotine, varenicline, and bupropion led to decreased levels of glucose-stimulated insulin secretion with each agent, suggesting that further studies to address these questions are needed [62].

The clear association between T2D risk and disease severity underscore the importance of promoting smoking cessation in indvidiuals with T2D. However, many persons with T2D continue to smoke, despite these contraindications. Increasing rodent and human evidence indicates that T2D may increase the rewarding effects of dopamine, as disrupted insulin

signaling during T2D suppresses dopamine signaling in the mesolimbic reward pathway [63].

Conclusions

Epidemiological studies demonstrate a clear association between cigarette smoking and an increased risk of T2D, whereas clinical data suggest an effect of smoking and nicotine on body composition, insulin sensitivity, and pancreatic β cell function. Human, rodent, and *in vitro* studies have begun to yield insight into the molecular mechanisms through which nicotine and smoking exposure impact glucose homeostasis. However, a complete understanding of the underlying pathways impacted by tobacco abuse, especially mechanistic studies focused on the pancreatic β cell, are lacking. Not withstanding these unknowns, this comprehensive review of available literature suggests that smoking should be elevated to the category of a recognized and modifiable risk factor for the development of diabetes, uniformly across all diabetes organizations and that smoking status should be considered as an indication for diabetes screening. Moreover, smoking cessation along with weight control post cessation should be promoted as an essential public health practice for diabetes prevention.

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