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Smoking Cessation And Diabetes

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Nicotine, when inhaled through the combustion of tobacco, is the most addictive drug known to mankind. One in five Canadians smoke cigarettes. The association between smoking and disorders such as cardiovascular (CV) and respiratory diseases, and carcinoma is well known; however, most clinicians and smokers are unaware of the association between smoking and the risk of developing type 2 diabetes mellitus (T2DM). This risk can also be increased by intrauterine exposure to tobacco smoke. It is estimated that 12% of T2DM can be accounted for by smoking. T2DM smokers have poor glycemic control, which is often due to a combination of nicotine-induced insulin resistance and a clustering of other risk factors (eg, poverty and lower education levels). On the other hand, Type 1 diabetic (T1DM) smokers have many more clinically significant hypoglycemic episodes. Diabetic smokers have a higher incidence of microvascular and macrovascular complications and premature mortality. It is clear that interventions are necessary to help smokers stop; however, when diabetic smokers quit they have difficulty maintaining glycemic control in the short term. Overall, given the synergistic effects of diabetes and smoking, it is imperative that smokers quit smoking to reduce their risk of developing diabetes and diabetic smokers need assistance to stop as soon as possible to reduce their risk of premature morbidity and mortality. This issue of *Endocrinology Rounds* examines tobacco smoking in Canada and the relationship with diabetes and glycemic control; further, the physiological effects of smoking and various treatment directions are discussed.

The smoking environment in Canada

Currently, 19% of Canadians over the age of 15 are smokers and approximately 59% of daily smokers have their first cigarette within 30 minutes of awakening.¹ This is an indication of the addictiveness of cigarettes, which causes smokers to reach for one before engaging in other activities due, in part, to acute withdrawal after a night of abstinence. Although more adult men than women smoke, there are no sex differences found in teenaged smokers. In Canada, although more smokers than ever have quit smoking, the health effects of smoking remain the single most preventable cause of death. It is estimated that 37,000 Canadians die from smoking per year;² as a result, smoking-attributable mortality accounts for 1 in 5 deaths, which is 5 times the deaths due to car accidents, suicides, other drug abuse, murder, and human immunodeficiency virus (HIV) combined.

Cigarettes are consumer products that kill 1 in 2 users when used as intended by the manufacturer.³ Current laws exempt the tobacco industry from any accountability for the damage caused due to a faulty product. Most mortality is due to CV disease and cancer, followed by respiratory disease.⁴ Smoking tobacco causes 85% of lung cancers and 1 in 5 smokers will develop lung cancer.⁴ Other conditions associated with smoking tobacco include macular degeneration, pancreatic cancer, bladder cancer, breast cancer, hepatocellular carcinoma in patients with hepatitis C, peripheral vascular disease, infertility, inferior birth outcomes, and sudden infant death syndrome (SIDS).⁵⁻⁹ It is also associated with poorer healing of wounds and fractures,^{10,11} however, smoking tobacco is also associated with a reduced risk of Alzheimer disease, Parkinson disease, and symptom severity in patients with ulcerative colitis.¹²⁻¹⁴ Nevertheless, 50% of deaths occur in the 44- to 50-year-old age group, leading to enormous burdens on families and society because these individuals die during their most productive period of life.^{15,16} Given that the risk of CV disease is most readily reversible, quitting smoking at any age may increase life expectancy; in fact, quitting smoking before the age of 30 leads to a normal life expectancy and even quitting at age 60 gains 3 years of life.¹⁶

Smoking as an addiction

Addiction is the continued use of a drug despite causing harm in several domains of life.¹⁷ All addictions, including smoking, are associated with habitual and ritualistic practices that



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must be extinguished to prevent relapse.¹⁸ Current evidence indicates that 50% - 60% of smoking behaviour can be accounted for by various genetic factors including nicotine metabolism and dopamine neurotransmission.^{19,20} However, it is the interplay of gene-gene and gene-environment interactions that determine whether a smoker will continue or attempt to stop smoking permanently.²¹

Does smoking cause diabetes?

Evidence for an association

The prevalence of smoking among patients with diabetes appears to mirror that of the general population;²² however, some investigators have found that cigarette smoking increases the risk of T2DM in the general population.²³⁻²⁶

Evidence from cohort studies

Recently, an excellent meta-analysis was published on cohort studies exploring the association between smoking and diabetes.²⁷ A pooled analysis of 25 international cohort studies met the inclusion criteria and resulted in a sample size of 1.2 million subjects. There were 45,844 newly diagnosed patients with T2DM, primarily from the United States (US), Japan, and Germany. The pooled, adjusted relative risk (RR) for diabetes in smokers was 1.44 (95% confidence interval [CI], 1.31-1.58). The association was evident across a series of sensitivity analyses and a stratified analysis of the data.

Previously, there were conflicting opinions regarding a dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.^{25,28-30} Some studies found such an association^{24,25,31} while others had not. In the meta-analysis by Willi et al,²⁷ the risk of diabetes was greater for heavy smokers (20 cigarettes/day; RR=1.61; 95% CI, 1.43-1.80) than for lighter smokers (RR=1.29; 95% CI, 1.13-1.48), and lower still for former smokers (RR, 1.23; 95% CI, 1.14-1.33) which is consistent with a dose-response phenomenon.

Passive exposure at any stage of development is associated with elevated risk

Passive tobacco exposure over 15 years in those who never smoked is a risk factor for glucose intolerance and the development of diabetes.²⁵ This is also relevant to intra-uterine exposure for a developing fetus. There is emerging evidence that *in utero* exposure to cigarette smoke is associated with the risk of developing insulin resistance and even T2DM in adolescence and adulthood.³²⁻³⁶ These effects are independent of other psychosocial risk factors and, although the exact mechanism is unknown, it is thought to be mediated through adult adiposity.³³ Pregnant women who smoke may be at an increased risk of developing gestational diabetes (adjusted odds ratio [OR] = 1.9, 95% CI, 1.0- 3.6).^{31,36} Altogether, these data suggest that smoking while pregnant affects not only the fetus, but also the mother for the risk of diabetes.

Causation

To examine the possibility that smoking causes T2DM, it is necessary to examine the evidence that fulfils the criteria outlined by Hill.³⁷ Several studies support a causal link with the risk of developing T2DM, and the strength of asso-

ciation is significant and consistent across several studies from different countries.^{29,38-43} Although there is a temporal relationship with smoking and diabetes, there is no specificity of smoking causing diabetes, since it causes several other diseases as well. Smoking increases insulin resistance that is mediated through nicotine in patients with T2DM.^{44,45} Smoking is also associated with other features involved in insulin resistance, such as postprandial hypertriglyceridemia, which is possibly due to the reduced clearance of triglyceride-rich chylomicrons and their remnants.^{42,46} Smoking has also been found to impair insulin sensitivity in healthy people.³⁹ In patients with diabetes, insulin sensitivity was found to decrease by 10%-40%; however, it normalized within 8 weeks of smoking cessation, despite a mean weight gain of 2.7 kg.³⁸ The effect of smoking on inhaled insulin absorption is reversed after only 1 week of smoking cessation.⁴¹ Contradicting the evidence in favour of a biological and temporal relationship is the observed increased incidence in the development of T2DM when smokers quit. Postcessation weight gain does increase the risk of developing T2DM for women during the first 5 years after quitting and after 10-20 years for men, but there is a reduction in the long-term overall risk.^{29,43}

The prospective risk of developing diabetes in both sexes is about 50%;⁴⁷ therefore, it is estimated that 12% of all T2DM in the US may be attributable to smoking.⁴⁸ However, there may be noncausal explanations, such as the clustering of unhealthy behaviours, particularly in lower socioeconomic groups. Observations also indicate that heavy smokers have higher body-mass indexes (BMIs) due to the repetitive cycle of stopping smoking, gaining weight, relapsing, and stopping again.⁴⁹ More studies are needed to better define the mediating mechanisms.

T1DM is not caused by smoking;⁵⁰ in fact, smoking reduces the risk of latent autoimmune diabetes in adults and of traditional T1DM.²⁶ This is probably due to the immunosuppressive effects of tobacco smoke; however, smoking does have an impact on glycemic control and subsequent complications. The majority of diabetic adolescent smokers initiate smoking after their diagnosis,^{51,52} and they also engage in more risky behaviours, including smoking.⁵³

Role of smoking in glycemic control

Diabetic patients who smoke are less likely to be active in self-care or to comply with diabetes-care recommendations compared with nonsmoking diabetic patients.⁴⁹ Smoking is a strong predictor for poor metabolic control.^{54,55} In 2004, a cross-sectional study of 61,890 T2DM patients from the Swedish National Diabetes Register, found that smoking was associated with increased levels of HbA_{1c}.⁵⁵ However, patients with T1DM who smoke have 2.6 times the odds of clinically significant hypoglycemic episodes than nonsmokers, even after controlling for confounding factors.⁵⁶

Effects of smoking on morbidity and mortality

Cigarette smoking increases mortality rates among individuals with diabetes in a linear dose-dependent manner.^{23,57} Heavier smoking doubles the risk of mortality compared with those who never smoked and most of these deaths are due to coronary heart disease (CHD),⁵⁸ but quitting smoking for ≥10 years will normalize mortality rates.²³

Smoking is associated with the development of microvascular and macrovascular complications in patients with diabetes due to a combination of effects on insulin resistance and direct effects on endothelial dysfunction and inflammation. The combined effects of smoking and diabetes appear to heighten the development of macrovascular complications.⁵⁹ Smoking is an independent risk factor for CHD and stroke, and it is associated with premature atherosclerotic disease in older patients with both T1DM and T2DM.^{47,60-62} Smoking is also related to premature development of multiple microvascular complications of diabetes such as nephropathy, neuropathy, and retinopathy.²³

Increased risk of nephropathy

Smoking increases the risk for developing microalbuminuria in diabetic patients.⁵⁵ Smokers have an albumin excretion rate 2.8 times that of nonsmokers even after controlling for glycemia, hypertension, duration of diabetes, age, and sex.⁶³ Moreover, the rate of progression was faster in smokers than in nonsmokers. Case-controlled and prospective studies with either a 13-year follow-up or biopsy-confirmed pathology clearly demonstrate smoking is an independent cause of impaired renal function.⁶⁴⁻⁶⁶

Association with diabetic neuropathy

Evidence is inconsistent regarding the association of smoking with the development of neuropathy. A case-controlled study in Iran of 110 patients with T2DM found no association.⁶⁷ However, a prospective European cohort study in 1,172 patients with T1DM found about 23% developed neuropathy within an average of 7 years.⁶⁸ Smoking was independently associated with the development of neuropathy.

Retinopathy

No consistent correlation has been found with retinopathy except in elderly smokers.⁴⁹ In a study of 996 T1DM patients treated with insulin, in those over 18 years, smoking was associated with central retinal arteriolar equivalent, central retinal venular equivalent, and arteriovenous (AV) nicking, but not with arteriole-to-venule ratio reduction or focal arteriolar narrowing.⁶⁹

Smoking cessation and diabetes

Smoking cessation is the most cost-effective intervention associated with a reduction in morbidity and mortality.^{70,71} Effective interventions causing 1 in 50 smokers to quit for >1 year are considered clinically significant.⁷² Despite these benefits, smoking cessation in patients with diabetes requires close monitoring. In a small case-control study in Japan, glycemic control and diastolic blood pressure deteriorated in T2DM patients after quitting smoking independent of the increase in BMI postcessation, but correlated with baseline BMI and triglycerides.⁷³ Blood sugars were $6.8 \pm 0.3\%$ before quitting smoking; $7.4 \pm 0.3\%$, 6 months after quitting smoking ($P < 0.05$); and $7.8 \pm 0.4\%$, 12 months after quitting smoking ($P < 0.001$).

There is evidence of a considerable desire to quit among smokers with diabetes.^{74,75} In one study, 70% of diabetic smokers received advice or help from a general practitioner (GP) to quit smoking; this help consisted

primarily of brief counselling, sometimes with nicotine-replacement therapy (NRT) or written materials.^{74,76} However, these diabetic smokers fare less well than non-diabetic smokers and may represent a population more resistant to standard smoking-cessation techniques.^{22,49} Some studies have indicated that these patients are less motivated to quit than smokers without diabetes.^{49,77} The majority do not participate in smoking-cessation groups and their drop-out rates are higher.⁷⁵ One explanation may be the elevated concerns about weight gain upon smoking cessation.^{57,74}

Smoking-cessation programs for diabetic smokers

Smoking-cessation programs should be individualized and implemented with a focus on specific cognitive, behavioural, and pharmacological therapies that control weight and prevent depression.^{57,78} Critical treatment characteristics should, at a minimum, include brief counselling, use of individual or group counselling, and pharmacotherapy. The protocol should consist of routine assessments of use, an assessment of interest in quitting, advice on the importance of quitting, assistance in setting a quit date, offering counselling and assistance, and arrangements for follow-ups.⁷⁸ Few studies focus specifically on integrated interventions for patients with diabetes who smoke. In one study, a brief, integrated smoking-cessation protocol demonstrated better results than usual care at 3 months, but not at 6 months.⁷⁹ A randomized, controlled clinical trial in 280 diabetic smokers, who were provided structured intervention by a trained nurse and followed by phone and mail contact in both primary care and hospital clinics, demonstrated a 17% quit rate in the intervention group at 6 months vs only 2.3% in controls.⁷⁵ Moreover, there was a significant reduction in the amount smoked in the intervention group compared with controls. This suggests that in specialized clinics where other health behaviours are addressed (eg, diet and exercise), intensive smoking strategies may lead to better outcomes.

Helping smokers with diabetes quit

Patients with diabetes are required to make significant health behaviour changes including modifying their diet, increasing physical activity, monitoring blood sugar, and adopting medication regimens.^{80,81} The demands for change and the accompanying stress may decrease the motivation to quit smoking while patients are adjusting to their diabetes. Therefore, it is important to work with patients to explore their motivation and examine the feasibility of addressing these behaviour changes over time.^{82,83} For some, quitting smoking is part of their comprehensive attempts to improve the management of their disease; for others, it is of less priority. Regardless, it is extremely important and effective for the physician to screen every patient regarding his/her smoking status and to advise all smokers to quit in clear and simple terms.^{84,85}

Assessing motivation

A clinician can quickly assess the level of motivation by asking the following questions.⁸⁶⁻⁸⁸

- **Importance:** Given everything going on in your life right now, on a scale of 1 to 10, where 10 is the most important thing to do, how important is it for you to quit smoking?

- **Confidence:** On a scale of 1 to 10 how confident are you that you will be able to quit smoking?

If the smoker has low confidence or gives low importance to quitting, the task of the clinician is to assist the patient to increase those domains before attempting to quit.⁸⁹ If the person is both confident and feels that it is important to quit smoking, the clinician should assist the person in developing a plan for a quit attempt and for maintaining his/her smoke-free status. The first step involves the patient appreciating that quitting is a process and not a singular event. If the person has tried and relapsed in the past, it is important for him/her to understand that this is part of the quitting process. The assessment requires an understanding of the smoking history of the patient and includes the level of dependence, previous quit attempts, and comorbid environmental, medical, and psychiatric factors that could affect outcome. All smokers should be invited to set a quit date within 30 days of the visit and use the intervening time to plan. This involves engaging supports in their social environment, making their home, work, and automobile smoke-free, and keeping a daily diary (much like a blood-sugar diary) of their smoking. They should also engage professional help from a doctor, nurse, pharmacist, or any other trained healthcare provider to assist with strategies for coping with cravings and breaking the habitual aspects of smoking. They may use distraction (eg, drinking a glass of milk or using sugarless candy) and/or delay (eg, waiting at least 20 minutes) tactics when faced with a craving to smoke. Moreover, avoiding the many triggers to smoke (eg, people, places, and things) in the first few months is also helpful, but not always feasible. Telephone quitlines staffed by trained personnel provide evidence-based counselling to smokers and are freely available across Canada.⁹⁰ More recently, evidence-based web-assisted tobacco smoking interventions have also become available.^{91,92}

Smoking-cessation medications

Several systematic reviews demonstrate that smoking-cessation medications double the odds of successful quitting in the long term compared with placebo.⁹³⁻⁹⁶ Based on the US Department of Health and Human Services (USHHS) guidelines,⁷⁸ some first-line medications have Grade A evidence for their recommendation. These include the various forms of NRT (patch, gum, inhaler, lozenge) and bupropion sustained release (SR). More recently, a Cochrane review has been completed on the benefits of varenicline and cytosine for smoking cessation;⁹⁵ therefore it is likely that these medications will be included in the 2008 revision of the USHHS guidelines.

There are two second-line medications – nortriptyline and clonidine – with Grade A evidence, but no official indication for smoking cessation.^{93,97} Rimonabant, a cannabinoid receptor 1 antagonist, has demonstrated weight-reduction benefits in obese diabetic patients,⁹⁸ but there have been conflicting effects on

smoking.⁹⁹ Although it attenuates weight gain at a dose of 20 mg/day, rimonabant is associated with the development of depression and suicidal ideation in some patients; currently, it is not available in Canada.

Cigarette smokers with diabetes typically have poor uptake, awareness, and knowledge of NRT and bupropion.⁷⁷ Moreover, those who are aware often think that the medication is dangerous to use. No single smoking-cessation medication has been proven more effective than another for this population.⁵⁷ Pharmacotherapy is indicated for motivated smokers who smoke ≥ 10 cigarettes per day.

NRT: NRT is available over-the-counter as transdermal patches, gums, lozenges, and inhalers in Canada. It is recommended that use begin on the day the person quits to attenuate withdrawal and continue for 10 weeks.¹⁰⁰ Recently, nicotine gum has been used to assist in tapering off smoking, and evidence suggests that starting NRT 1 week prior to quitting is more effective.¹⁰¹

Use of NRT for a longer time than intended may lead to increased levels of insulin resistance and hyperinsulinemia, which are risk factors for CV problems and T2DM.¹⁰² However, long-term nicotine use is associated with elevated circulating leptin levels and may explain the weight reduction in smokers and nicotine gum users.¹⁰³ Leptin levels return to normal after stopping nicotine, which is associated with postcessation weight gain. Given the complex effects on insulin resistance, it is recommended that the use of NRT therapy in diabetic patients for smoking cessation be transient and limited.⁵⁷

Bupropion: Bupropion has been found to double quit rates, independent of its effect on mood.⁹⁶ It probably acts as a partial nicotine antagonist, although the exact mechanism of action is unknown.¹⁰⁴ Bupropion is orally bioavailable and should be started while the patient is still actively smoking and continued for 12 to 52 weeks. It may be advantageous in patients with diabetes, since it is associated with the least weight gain and can also treat any underlying depression, which is significant in this population.⁷⁷

Varenicline: Varenicline, a partial alpha4 beta2 nicotinic receptor antagonist is a specific treatment for smoking cessation that revealed superior efficacy at the end of treatment (12 weeks) compared to bupropion, but not at one year.⁹⁵ The dual action of varenicline reduces withdrawal and blocks the pleasurable effects of smoking. It is started at least 1 week before the person attempts to quit and is continued for 12 weeks. Responders who are prescribed an additional 12 weeks are more likely to remain abstinent at 1 year compared with those given placebo;¹⁰⁵ however, varenicline has not been studied in diabetic smokers. There is one case report of severe hypoglycemia in a patient with T1DM that returned to normal with the discontinuation of the medication.¹⁰⁶

Conclusion

NRT should be used at the lowest effective dose for 10 weeks. Bupropion may be more appropriate because it causes the least weight gain when smokers quit and relieves the depressive symptoms that are prevalent in diabetic smokers. Varenicline is currently the most efficacious medication in smoking cessation; however, no large-scale trials have been done in diabetic populations. Other promising medications include CB₁ receptor antagonists (eg, rimonabant) that may reduce smoking in the short term, while having modest effects on insulin resistance and obesity.

Smoking cessation is very important for the prevention of diabetes; in patients with diabetes cessation will help to prevent the associated excess morbidity and mortality that results from this devastating disease. Nevertheless, careful metabolic monitoring is warranted for all patients quitting smoking.

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