

Managing vascular risk factors among obese quitters with diabetes: how intensive lifestyle intervention and novel pharmacotherapy can work in concert

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Abstract

Obese smokers with diabetes are a special risk category for all-cause mortality and major adverse cardiovascular events (MACE). Weight loss and smoking cessation are key interventions advocated for the management of diabetes in almost all the guidelines across the globe. However, there is a substantial risk of weight gain following smoking cessation which may, in some cases, cause a transient worsening of glycaemic control in people with diabetes. The risk of weight gain and the potential for worsening of HbA_{1c} may put off some obese smokers to quit. The cardiometabolic sequelae of smoking cessation in people with and without diabetes are different. The benefit of smoking cessation, in terms of reduced cardiovascular and all-cause mortality, in people without diabetes is evident within three years of quitting. However, it may take up to 10 years for people with diabetes to get this benefit. Post-cessation weight gain is much more detrimental to obese quitters with diabetes than those without. The aim of this review is to explore how best these high-risk individuals can be supported to remain abstinent long-term, and manage their vascular risk profile proactively, by concerted lifestyle intervention with judicious use of new and novel pharmacotherapy.

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Key words: diabetes, obesity, vascular risk factors, quitting

Background

Obese smokers constitute a special risk group for the vascular complications of diabetes. A constellation of aetiologically linked pathophysiological processes contributes to the higher prevalence of microvascular and macrovascular complications in obese smokers

with diabetes.^{1,2} Insulin resistance appears to be the linking thread between obesity, smoking and type 2 diabetes (T2DM), which are often accompanied by hypertension, dyslipidaemia and endothelial dysfunction.³ Smoking is considered to be closely associated with insulin resistance, which appears to potentiate the vascular risk profiles in obese people with T2DM.⁴ Several studies have shown that both smoking and obesity accelerate insulin resistance and β -cell apoptosis.⁵⁻⁷ Interestingly, as the global prevalence of obesity is rising, so is the prevalence of diabetes, hypertension and dyslipidaemia, suggesting that obesity, T2DM, hypertension and dyslipidaemia might have a common and shared pathophysiology.^{8,9} Both obesity and smoking impact on several key portals of glucose, lipid and blood pressure regulating mechanisms, leading to hyperglycaemia, dyslipidaemia and hypertension, which are key precursors for both macrovascular and microvascular complications in diabetes. A recent systematic review and meta-analysis by Pan *et al* revealed that smokers with T2DM have a significantly higher rate of all-cause mortality and vascular complications than non-smokers with T2DM.¹⁰ Similar associations have been found in obese people with T2DM, who have a higher prevalence of microvascular and macrovascular complications than non-obese individuals with diabetes.^{9,11}

The objective of this review is to evaluate the impact of smoking cessation on the vascular risk profiles of obese people with diabetes, and to explore how the new and novel pharmacotherapy can play a complementary role in association with aggressive lifestyle intervention. Important lifestyle interventions like smoking cessation should continue to be at the centre of the management of diabetes, as the risk of diabetic complications is significantly higher in smokers than in non-smokers.^{12,13}

Relationship of obesity, smoking and vascular risk profiles

Obesity follows a trajectory of interlinked metabolic disarray from insulin resistance, fasting hyperglycaemia and impaired glucose tolerance, leading to T2DM.¹⁴ Smoking seems to play a contributory role in all the phases of this trajectory. In addition to expediting insulin resistance – and its subsequent sequelae on glucose – and lipid metabolism, obesity and smoking are considered to be independent risk factors in macroangiopathy and microangiopathy.^{15,16} Obesity is linked with hypertension in

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people with or without diabetes.¹⁷ Smoking is also associated with an acute rise in blood pressure and an accelerated rate of vasculopathy in people with diabetes.¹⁸⁻²⁰ Both obesity and smoking are linked with atherogenic dyslipidaemia, which are considered to be the forerunners of vascular complications in diabetes.^{21,22} Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that an effective management of hypertension, dyslipidaemia, obesity and smoking cessation are as important as – if not more than – glycaemic control in the management of diabetes.^{23,24} Most recently, 21-year follow-up data on the original cohort of the STENO-2 study demonstrated an average increase of 7.9 years of life expectancy in the group who received a target-driven multifactorial intervention compared with conventional treatment.²⁵ Smoking cessation was one of the key components of this multifactorial intervention.

However, a recent systematic review and meta-analysis of a large cohort (n=101,000) of smokers, non-smokers and quitters with diabetes demonstrated that there was a graded relationship between quitting smoking and decline in HbA_{1c}; the longer the duration of abstinence, the lower the HbA_{1c}.²⁶ A retrospective study on The Health Improvement Network (THIN) database by Lycett *et al* showed that the HbA_{1c} could rise for up to about three years after smoking cessation compared with continued smokers in people with T2DM.²⁷ A recent World Health Organization (WHO) study showed that the risk of all-cause mortality was higher for recent quitters (1–9 years) than for those who quit earlier (>10 years) compared with non-smokers. The relative risk of all-cause mortality in these two groups was 1.53 (95% CI 1.19 to 1.97; p=0.001) and 1.25 (95% CI 1.03 to 1.52; p=0.02), respectively.^{28,29}

Impact of quitting and weight loss in obese smokers with T2DM

Several studies have shown improved cardiometabolic profiles following smoking cessation and weight loss in people with diabetes. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon modified release Controlled Evaluation) trial with 11,140 participants with T2DM demonstrated a 30% reduction in all-cause mortality after smoking cessation.² The Nurses' Health Study also showed a significant improvement in all-cause and cardiovascular mortality after smoking cessation in those with T2DM.³⁰ Studies have shown that the benefit of quitting is precipitously reflected upon people without diabetes, as evidenced by reduced cardiovascular mortality, to the level of non-smokers within three years after quitting.³¹ However, the benefit of quitting and mortality is not so prompt in quitters with diabetes. The Multinational Study of Vascular Disease (MSVDD), a large epidemiological study, demonstrated that it might take up to 10 years for the cardiovascular mortality in quitters with diabetes to reach the level of non-smokers.²⁸

Similar benefits can be gained by weight loss in obese people with T2DM. Weight loss in obese smokers improves a number of cardiometabolic parameters. Insulin sensitivity seems to improve significantly even with moderate weight loss, which is

reflected on the HbA_{1c} and lipid profile. The Look AHEAD trial examined the influence of weight loss on obese people with T2DM.³² After four years of follow-up, obese and overweight people with T2DM managed to lose 6.15% of body weight from baseline by intensive lifestyle intervention while the control group, with standard diabetes support and education, managed to lose 0.88%. These two groups showed a difference in a number of cardiometabolic parameters including HbA_{1c} (–0.36% vs. 0.09%, p<0.001), systolic blood pressure (–5.33 vs. –2.97 mmHg, p<0.001), diastolic blood pressure (–2.92 vs. –2.42 mmHg, p<0.012), HDL cholesterol (3.67 vs. 1.97 mg/dL, p<0.0001) and triglyceride level (–25.56 vs. –19.75 mg/dL, p<0.0006). The longer the weight loss was sustained, the better was the cardiovascular outcome.^{32,33}

Barriers to smoking cessation in obese smokers

Despite an all-out drive worldwide to discourage smoking in people with T2DM, the prevalence of smoking in people with and without diabetes remains comparable.³⁴ The risk of further weight gain and worsening glycaemic control are the commonest arguments against quitting. In a recent systematic review and meta-analysis, Tian *et al* demonstrated that, by the 12th month after quitting, the average weight gain was 4.10 kg.³⁵ There was some anecdotal evidence that this weight gain might perpetuate a rise in HbA_{1c}.^{27,36} However, there is undisputable evidence to suggest that post-cessation weight gain and its adverse effects on HbA_{1c} can be offset by incorporating quitting as part of a structured lifestyle intervention.^{37,38}

Intensive lifestyle intervention following smoking cessation

Structured lifestyle interventions have consistently shown promising prospects of mitigating the weight gain in quitters with T2DM. A community-based cohort study on the Framingham Offspring Study demonstrated that recent quitters with diabetes gained more weight than quitters without diabetes; median weight gain was 3.6 kg (IQR –1.4 to 8.2) and 2.7 kg (IQR –0.5 to 6.4), respectively.³⁹ Stamford *et al* demonstrated that, following smoking cessation, the average daily caloric intake was increased by 277 kcal without any increase in physical activities.⁴⁰ The study postulated that 69% of this post-cessation weight gain was attributed to increased calorie consumption, and the remaining 21% was due to the downregulation of basal metabolic rate. Interestingly, if an exercise programme equivalent to about 45 minutes of extra walking a day accompanied the smoking cessation programme, this weight gain could be reduced to 1.3 kg over a two-year period.⁴¹ Integrating behavioural therapy to include dietary intervention, and promoting physical activities alongside pharmacotherapy, not only offset the weight gain but also increased the quit rate from 2–5% to 15–20%.^{42,43} Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) is a very successful integrated lifestyle intervention model.^{44,45} In recent obese quitters with diabetes, a DESMOND plus model (new and novel pharmacotherapy plus DESMOND) could be a step forward in the traditional smoking cessation programme.

New and novel pharmacotherapy

In the last 10 years, significant progress has been made in the field of pharmacotherapy to reduce the vascular risk factors in people with diabetes. Metformin is an effective initial oral medication for obese smokers with T2DM because of its combined hypoglycaemic and cardioprotective properties. Multiple studies have demonstrated that metformin has a beneficial role on vascular risk profiles over and above its glucose-lowering effects.^{46,47} The American Diabetes Association and the European Association for Study of Diabetes published a joint statement recommending metformin as the first-line treatment for obese people with diabetes.^{48,49} In a recent study, the researchers have demonstrated that smokers who were on metformin had an 8% increased risk of major adverse cardiovascular events (MACE) compared with 32% for those who were not on metformin.⁵⁰ Similarly, in the Biguanides and Prevention of the Risks of Obesity (BIGPRO) trial, participants who were on metformin achieved significantly more weight loss than those who were on placebo (−2.0 kg and −0.8 kg, respectively).⁵¹ Therefore, we can conclude that, in obese current and ex-smokers with T2DM, concurrent treatment with metformin attenuates the observed higher risk of MACE and all-cause mortality.

However, if metformin is not tolerated or contraindicated, sulfonylureas should be considered with caution as an alternative agent. Sulfonylureas are obesogenic drugs and can cause hypoglycaemia, which can be a deterrent to quitting and to remaining abstinent.⁵² A better option for pharmacotherapy could be other novel glucose-lowering agents which are weight neutral or have weight-reducing properties, such as sodium glucose co-transport-2 (SGLT-2) inhibitors and incretin-based agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonist (GLP1-RA).

SGLT-2 inhibitors are a group of orally administered glucose-lowering drugs which are not insulin dependent and therefore do not cause hypoglycaemia and weight gain.⁵³ A recent meta-analysis comparing SGLT-2 inhibitors with placebo showed that the mean reduction in HbA_{1c} with SGLT-2 inhibitors was −0.66% compared with placebo and the mean weight loss with SGLT-2 inhibitors was −1.8 kg compared with placebo. A similar outcome was noted for blood pressure in another meta-analysis comparing SGLT-2 inhibitors. Compared with placebo, the mean reduction in systolic and diastolic blood pressure with SGLT-2 inhibitors was −4 mmHg and −1.6 mmHg from baseline, respectively.⁵⁴ For obese quitters, this group of drugs can be considered in preference to insulin secretagogues.

Incretin-based drugs GLP1-RA and DPP-4 inhibitors are a group of glucose-lowering drugs which have additional weight-reducing or weight-neutral effects. They can be used as suitable agents to deal with the weight gain following smoking cessation in obese smokers with T2DM. GLP-1RA delivers a supra-physiological level of GLP-1, resistant to biodegradation by endogenous DPP-4. In addition to glycaemic control, GLP-1RAs are useful agents for weight loss, control of blood pressure and managing dyslipidaemia.⁵⁵ DPP-4 inhibitors, on the other hand, are weight-neutral glucose-lowering drugs with a favourable outcome on a number of cardiovascular risk factors including HbA_{1c} and lipid



Key messages

- The cardiometabolic sequelae of quitting are different in people with and without diabetes
- Further weight gain and a transient deterioration of glycaemic control in obese smokers can be challenging after quitting
- Quitting smoking for <10 years does not provide any meaningful cardiovascular protection for obese smokers with diabetes
- Smoking cessation should be offered as part of a structured multifactorial intervention package such as DESMOND
- Judicious use of new and novel therapy for a selected group of quitters can help to keep them abstinent while improving their overall vascular risk profiles

profile.⁵⁶ A recent meta-analysis compared GLP-1RAs and DPP-4 inhibitors for their glucose-lowering efficacy and weight-reducing properties. Long-acting GLP-1RAs showed a greater reduction in HbA_{1c} from baseline than DPP-4 inhibitors. Both short- and long-acting GLP-1RAs were associated with significant weight loss from baseline, while DPP-4 inhibitors were associated with a trend towards weight loss.⁵⁷

Conclusion

Obese smokers with diabetes are a special risk category before and after smoking cessation. They should be actively supported to quit and remain abstinent long-term. Smoking cessation should be offered as part of a structured multifactorial intervention strategy. A targeted multifactorial intervention alongside a judicious use of non-insulin-based glucose-lowering agents with added weight-neutral or weight-reducing properties will help to avert the weight gain and its deleterious impact on glycaemic control. In order to address the dyslipidaemia and associated risk of adverse cardiovascular events, this group should be treated aggressively with HMG Co-A reductase (statin therapy) inhibitors.

Conflict of interest None.

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