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Review

Cigarette smoking, type 2 diabetes mellitus, and glucagon-like peptide-1 receptor agonists as a potential treatment for smokers with diabetes: An integrative review

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ABSTRACT

Tobacco use disorder (TUD), in particular cigarette smoking, contributes significantly to the macro- and micro-vascular complications of type 2 diabetes mellitus (DM). Persons with DM who regularly use tobacco products are twice as likely to experience mortality and negative health outcomes. Despite these risks, TUD remains prevalent in persons with DM. The objective of this integrative review is to summarize the relationship between TUD and DM based on epidemiological and preclinical biological evidence. We conclude with a review of the literature on the glucagon-like peptide-1 (GLP-1) as a potential treatment target for addressing comorbid TUD in smokers with DM.

Abbreviations: CO, carbon monoxide; CPA, conditioned place aversion; CPP, conditioned place preference; CVD, cardiovascular disease; CAD, coronary artery disease; EPM, elevated plus maze; eNOS, endothelial nitric oxide synthase; XR, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA1C, glycosylated hemoglobin; HFD, high fat diet; IL-6, interleukin 6; IPN, interpeduncular nucleus; MHb, medial habenular; NRT, nicotine replacement therapy; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; OR, odds ratio; PPG, preproglucagon; RA, receptor agonist; RD, regular diet; RR, relative risk; STZ, streptozotocin; DM, type 2 diabetes mellitus; TUD, tobacco use disorder; TNF-α, tumor necrosis factor alpha; VTA, ventral tegmental area

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Contents

1. Introduction

Tobacco use disorder (TUD), in particular cigarette smoking, is the leading cause of *preventable* morbidity and mortality in the United States and is associated with over 400,000 deaths annually. Deaths among non-smokers exposed to second-hand smoke account for an additional 50,000 deaths per year. Over 16 million Americans suffer from various chronic diseases caused by smoking. Medical care associated with addressing these chronic diseases approaches $170 billion and over $156 billion in lost productivity annually [1].

Another major public health problem is the exponential rise in the incidence of type 2 diabetes mellitus (DM) [2]. DM is a complex metabolic disorder caused by a combination of genetic and environmental determinants and associated with an array of negative physical and emotional outcomes, including macro- and micro-vascular diseases, depression, pain, and cognitive impairment. Besides the direct effect of DM on patients' lives, there is a substantial financial impact of the disease on society at large. Similar to TUD, medical care for DM is estimated to cost $176 billion with an additional $69 billion in reduced productivity [3,4].

Comorbidity of TUD and DM is a double health hazard [5]. In persons with DM, smoking may contribute to greater insulin resistance, worsened beta-cell function, endothelial dysfunction, and sustained low-grade inflammation, thereby exacerbating the macro- and micro-vascular complications of DM [5]. DM patients who smoke tend to develop vascular complications more often than non-smoking patients due to an increased risk of central obesity caused by smoking through antiestrogenic effect [6]. Obesity impedes glucose control by increasing insulin resistance through multiple factors including excess free fatty acids, increased release of cytokines from adipose tissues, and inflammation [7–9]. Apart of exacerbating hyperglycemia, smoking also affects vasculature directly by accelerating atherosclerotic lesions formation and impairing endothelial function of blood vessels throughout the body by increasing inflammation and oxidative stress [10–14]. Smoking also tends to accelerate the decline in renal function, causing structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis, and endothelial expansion [15,16].

Persons with DM who smoke are at higher risk of onset and progression of nephropathy [17–19], metabolic syndrome [20], coronary artery disease [20–23], and stroke [22,24,25]. Persons with DM who regularly use tobacco products are twice as likely to experience mortality and negative health outcomes [26,27]. The healthcare costs associated with treating DM in smokers are a staggering 300% higher than the costs of treating DM complications in non-smokers [28].

The goal of this review is to focus on new directions for treating this public health comorbidity. We first present an overview on the epidemiological association between smoking and incident DM. We then review potential biological mechanisms linking tobacco use and nicotine dependence with DM. We then discuss treatment of TUD and persons with DM, including pharmacotherapy with glucagon-like peptide 1 to address this comorbidity.

2. Cigarette smoking and DM

2.1. Clinical and epidemiological studies

The relationship between smoking and DM is likely to be bi-directional, that is, smoking may contribute to the development of DM, and patients with established DM may have a heightened propensity to smoke and less motivation to quit.

Table 1 summarizes outcomes from meta-analyses of epidemiological studies on the risk of DM in people who smoke. Willi and colleagues [29] reviewed 25 prospective cohort studies published up to 2007 and found a dose-response association between active smoking and incident DM, with the relative risk of DM greatest for current heavy smokers (≥20 cigarettes per day) compared to never-smokers, followed by current light smokers (<20 cigarettes per day), and lowest for former smokers. The authors noted, however, that other factors, such as stress, diet, and activity levels may have contributed to the association [29]. Of note, on the basis of this review, Ding and Hu (2007) estimated that 12% of all DM cases in the U.S. may be attributable to smoking [32].

Table 1 – Meta-analytic reviews of epidemiological studies showing a dose-response relationship between active smoking and incident DM.

Reference (publication year).	Number of included studies (total sample size, incident DM cases)	Relative risk of incident DM (compared to never-smokers)
Willi et al. (2007) [29]	25 studies (N = 1.2 million participants, 45,844)	<20 cigs/day: RR = 1.29 (1.13–1.48) ≥20 cigs/day: RR = 1.61 (1.43–1.80)
A Report of the Surgeon General (2014) [30]	51 studies (N = >3.9 million participants, 140,813)	Light smokers (<20 cigs/day in most studies): RR = 1.25 (1.14–1.37) Heavy smokers (≥20 cigs/day in most studies): RR = 1.54 (1.40–1.68)
Pan et al. (2015) [31]	88 studies (N = 5.9 million participants, 295,446)	<20 pack-years: RR = 1.21 (1.10–1.33) 20–39 pack-years: RR = 1.34 (1.27–1.41) ≥40 pack-years: RR = 1.57 (1.47–1.66)

A meta-analysis included in the most recent Report of the Surgeon General [30] examined data from 51 prospective cohort studies published up to 2010. Consistent with the meta-analysis by Willi et al. [29], the results indicated a dose-response relationship between active smoking and DM, with the relative risk of DM greatest for currently heavy smokers (≥20 cigarettes per day in most studies) compared to never-smokers, followed by current light smokers (<20 cigarettes per day in most studies), and lowest for former smokers. The association persisted and remained significant in all stratified analyses by various study and participant characteristics.

Similarly, in a review of 88 prospective cohort studies published up to 2015, Pan and colleagues [31] reported a dose-response between active smoking and incident DM, with the risk of DM for current smokers (relative to never smokers) increasing as a function of pack-years of smoking. Based on this meta-analysis, the authors estimated that smoking accounted for 10.3% of male and 2.2% of female DM cases for a total of approximately 25 million DM cases attributable to smoking worldwide.

A cross-sectional study of 2142 healthy adults aged 25–41 years conducted in Europe (Principality of Liechtenstein) assessed the relationship between cumulative smoking exposure and pre-diabetes [33]. In multivariable regression models, current smokers had a significantly increased risk of pre-diabetes (odds ratio (OR) = 1.82, 95% CI, 1.39–2.38). Persons with a smoking exposure of less than 5 pack-years, 5–10 pack-years, and greater than 10 pack-years had ORs for pre-diabetes of 1.34 (95% CI, 0.90–2.00), 1.80 (95% CI, 1.07–3.01), and 2.51 (95% CI, 1.80–3.59), respectively, compared with never-smokers. The substantially greater OR of this population-based analysis compared to the other larger studies are alarming, but the study was limited by its cross-sectional design and relatively smaller sample size. Further investigations need to examine whether smoking has a stronger association with pre-diabetes than with fully manifested DM, where the contribution of other lifestyle variables can be more difficult to separate from smoking's contribution.

A limited number of studies have compared trends in smoking prevalence among people with and without DM. Fan and colleagues [34] analyzed data from a large USA state-based telephone survey of non-institutionalized adults, collected from 2001 through 2010, and found the adjusted prevalence of cigarette smoking among adults with DM was 9% less than among adults without DM, which seems to contradict the previous associations. However, declines in smoking prevalence were greater among persons without DM ($P < 0.001$), indicating a sustained use of tobacco in persons with DM. Another study on trends in tobacco use among US adults utilized data from 9 years (2005–2013) of the U.S. National Survey on Drug Use and Health [35]. The investigators reported that cigarette smoking in adults is declining overall, however, smoking among those with DM and other chronic diseases is not declining. Thus, smoking appears to be more difficult to stop among DM patients, and they may need more targeted and intensive treatment resources, including pharmacological interventions which are different from those offered to smokers without DM.

2.2. *Preclinical studies: the reinforcing effects of nicotine in DM models*

Animal models of DM provide ways to investigate mechanisms contributing to greater tobacco use in patients with DM [31,36]. Much of this work suggests that this vulnerability could be due to the enhanced reinforcing effects of nicotine in the DM patients. For example, O'Dell et al examined the reinforcing effects of nicotine in DM rats induced by streptozotocin (STZ), a drug that is toxic to pancreatic beta-cells [36]. Results showed that STZ-treated rats exhibited increased self-administration of nicotine in a dose-dependent manner. Richardson et al examined whether insulin resistance, produced by a high fat diet (HFD) regimen, enhances the rewarding effects of nicotine, as measured by the conditioned place preference (CPP) paradigm [37]. Rats were placed on either a regular diet (RD) or HFD for 5 weeks and were subsequently assessed for insulin resistance via blood glucose measurements after insulin challenge. Increases in body weight were similar across all HFD-fed animals; however, HFD resulted in both insulin-resistant and non-insulin resistant animals. Notably, the magnitude of nicotine CPP was larger in insulin-resistant rats versus RD rats, whereas nicotine CPP was absent in non-insulin resistant HFD animals, suggesting that disruption of insulin signaling could mediate the reward-enhancing effects of nicotine.

Another study examined the rewarding effects of nicotine as well as the aversive effects of nicotine withdrawal using the CPP paradigm and the conditioned place aversion (CPA) paradigm, respectively [38]. CPA and physical signs of withdrawal were evaluated after administration of mecamylamine, a nicotine receptor antagonist, to precipitate withdrawal. The experimenters then utilized the elevated plus maze (EPM) procedures to assess anxiety-like behavior produced by nicotine withdrawal. Results showed that compared to vehicle-treated controls, STZ-treated (DM) rats displayed greater rewarding effects of nicotine and a larger magnitude of aversive effects and physical signs produced by withdrawal. In addition, STZ-treated rats displayed higher levels of anxiety-like behavior on the EPM during nicotine withdrawal. Although preliminary, these rodent studies suggest that increased rates of smoking in diabetics could be due to the enhancement of nicotine's reinforcing and withdrawal effects. Future studies in humans should assess this possibility.

2.3. *Smoking cessation in persons with DM*

Smoking cessation is a priority for reducing the combined health effects of TUD and DM, however barriers to quitting exist in this vulnerable group of patients. In smokers with or without DM, weight gain can be a major adverse effect of smoking cessation [39,40], resulting in worsening health conditions. However, in patients with DM weight gain may have a greater deterrent effect, especially in women [41–43]. For example, in a study of pharmacotherapeutic aids for smoking cessation in smokers with and without DM, Gill et al. [44], reported that compared to smokers without DM, smokers with DM had lower quit rates and displayed greater concern about weight gain following smoking cessation.

In addition to weight gain, smoking cessation can impact metabolic profile and glycemic control. Studies report that initially smoking cessation is associated with the deterioration of glycemic control, both in previously non-DM and DM persons. After 3 months (132 ± 16 days) of abstinence, previously non-DM participants exhibited fasting insulin resistance and increased beta cell secretion of insulin in response to glucose challenge [45]. No data were provided in the report regarding insulin sensitivity or beta cell function at later time points (after 3 months of abstinence), thus it is unclear how long the metabolic changes following smoking cessation persisted.

A recent study funded by the National Institutes of Health evaluated the relationships between smoking cessation, weight change, and new-onset DM in three cohort studies. The results indicated that the risk of DM was higher among recent quitters (2–6 years since quitting smoking), peaked at 5–7 years after quitting, and then gradually decreased. In that study, the increase in the DM risk was directly proportional to post-cessation weight gain and was not increased among quitters without weight gain ($P < 0.001$ for interaction) [46]. A study conducted in Taiwan found that the risk of new-onset DM increased within the first two years of abstinence, independent of weight gain [47]. In that study, the relative risk of DM was 1.50 (95% CI, 1.15–1.96) in current smokers, 1.83 (95% CI, 0.91–3.69) in former smokers in their first year of abstinence, and 2.02 (95% CI, 1.03–3.96) in their second year of abstinence compared to never smokers, However, the risk gradually decreased to null after three years of abstinence. In summary, smoking cessation is associated with an increased risk for developing DM during the first two years of abstinence, and the time it takes for this risk to attenuate appears to be at least 3 years with some variation among the studies.

In DM patients, smoking cessation may worsen glycemic control. Iino and colleagues [48] reported a significant change in HbA1C levels among DM patients increasing from 6.8 ± 0.3% before quitting to 7.4 ± 0.3% ($p < 0.05$) at month 6 and to 7.8 ± 0.4% ($p < 0.001$) at month 12 after quitting. In another study of 10,692 smokers with DM from a large UK primary care database, HbA1C increased by 0.21% within the first year after quitting, and this increase was not mediated by weight change [49]. In that same study, HbA1C gradually decreased, but remained higher compared to continuing smokers during the first 3 years after quitting. The consequences of smoking cessation on glycemic control and insulin resistance in patients with DM underscore the need for close glucose monitoring with targeted risk reduction interventions during the first few years after quitting [50].

In the long-term, smoking cessation appears to have a positive impact on a variety of other health outcomes in DM patients besides this persistent insulin resistance. Most notably, smoking cessation is beneficial in decreasing cardiovascular risk [51–53]. In a multi-center trial of 11,140 men and women with DM, quitting smoking was associated with 30% reduction of all-cause mortality, with the benefits for reduction of cardiovascular events being greater in patients who have quit smoking for over 10 years [53]. In another study (n = 6547), female nurses with DM who stopped smoking for ≥10 years, had a relative risk of coronary artery disease (CAD) of 1.01 (95% CI, 0.73–1.38), similar to that of nurses with DM who had never smoked [54]. A recent meta-analysis of 89 cohort studies concluded that although former smokers still have a higher risk of total mortality and cardiovascular events in comparison with never smokers, these risks are significantly lower than the risks in current smokers, suggesting substantial benefits of smoking cessation on total mortality and cardiovascular events for DM patients [55]. In summary, the evidence is consistent to conclude that smoking cessation reduces the macro-vascular complications of DM [50].

Smoking cessation appears to ameliorate the progression of diabetic nephropathy [56–58]. A large trial reported that compared to never smoking, daily smoking was associated with a 30% increased risk of diabetic nephropathy. More importantly, the risk of diabetic nephropathy was not significantly greater in former smokers than in non-smokers, suggesting that stopping smoking can stop the progression of nephropathy [53].

Despite the potential benefits of smoking cessation, few studies have evaluated the effect of smoking cessation interventions specifically in patients with DM. One recent trial [59] conducted in Canada tested the effectiveness of a practice-level intervention for smokers with DM (84%) and prediabetes (16%). The intervention consisted of counseling, discount cards (Can $150) to partially cover the cost of smoking cessation medication (NRT, bupropion or varenicline) and follow-

up telephone calls over a 6-month period. While the intervention improved long-term abstinence, the 6-month abstinence rates observed in the trial were lower than abstinence rates observed in trials of patients with other chronic diseases, such as heart [60] or pulmonary disease [61]. An earlier study which offered smokers with DM a consultation with a physician specialized in tobacco cessation and a prescription for NRT also emphasized greater difficulties with smoking cessation in DM than in those with other chronic diseases [26]. Thus, quitting appears to be more difficult in patients with DM than with other chronic diseases or with no chronic disease perhaps due to a difference in the underlying neurobiology of nicotine reinforcement among those with DM. We will return to this potential difference in the mechanism of nicotine reinforcement among DM smokers, and suggest a particular intervention that addresses this neurobiological difference in DM.

Further evidence for the efficacy of standard treatments for smoking cessation in DM includes a meta-analysis [62] published in 2014, which notably did not include any trials using varenicline. This meta-analysis failed to show efficacy for smoking cessation interventions in DM patients. However, the review included a relatively small number of trials published to date and a relatively small number of participants in the published trials (total N = 872). Of the 8 trials included in the meta-analysis, 5 assessed non-pharmacological interventions while 3 included optional nicotine replacement therapy without bupropion (2 trials) or with bupropion (1 trial).

Not including varenicline in that earlier meta-analysis seems critical, because a more recent study performed a retrospective pooled analysis of data on smokers with DM who participated in Pfizer-funded varenicline trials [63]. This analysis showed that varenicline was effective and well tolerated in DM patients, however, the number of participants with DM in the trials was small (total N = 323 DM patients; varenicline n = 162, placebo n = 161). That same report showed that continuous abstinence rates in patients with DM were consistently lower than those in non-DM patients. Specifically, at weeks 9–12, the OR was 2.26 (95% CI, 1.47–3.79) in DM patients versus 3.91 (95% CI, 3.49–4.37) in non-DM patients; at weeks 9–24, the OR was 2.25 (95% CI, 1.27–4.00) in DM patients versus 3.24 (2.83–3.72) in non-DM patients; and at weeks 9–52, the OR was 2.00 (95% CI, 0.90–4.49) in DM patients versus 3.07 (95% CI, 2.54–3.71) in non-DM patients. As noted above, data showing effective interventions for smoking cessation in patients with DM are limited [63], however, the findings of the existing studies suggest that conventional smoking cessation therapies, including varenicline, may be less effective in diabetic smokers and that new and more intensive treatments are needed for these comorbid patients.

3. Glucagon-like peptide-1 (GLP-1)

As suggested above, a difference in the underlying neurobiology of nicotine reinforcement among those with DM may contribute to the failure of currently available, evidence-based medications for those with DM. The following sections review an alternative approach to pharmacotherapy for smoking cessation in DM based on neurobiology of the glucagon-like peptide-1 (GLP-1) and its role in brain reinforcement from smoking in DM patients.

Incretin GLP-1 is secreted by intestinal epithelial endocrine L-cells [64] in response to nutrient ingestion [65]. GLP-1 stimulates insulin secretion from pancreatic beta cells in a blood glucose level-dependent manner [66] and suppresses glucagon secretion from alpha cells, thereby leading to a decrease in blood glucose levels. It also slows gastric emptying, improves insulin sensitivity, stimulates beta-cell regeneration and prevents beta cell apoptosis [67,68]. GLP-1 receptor agonists (RAs) are currently used for the treatment of DM, and Liraglitude (Saxenda®) is FDA approved for the treatment of obesity. These agents reduce glucose and weight by increasing glucose-dependent insulin secretion and decreasing glucagon secretion, delaying gastric emptying, and increasing satiety [69–71]. GLP-1 RAs demonstrate significant reductions in HbA1C levels and generally have a favorable effect on weight and minimal risk of hypoglycemia.

GLP-1 receptors are present not only in the pancreas, but also in the heart, blood vessels, stomach, intestines, visceral fat, kidney, and the brain, notably reinforcement pathways stimulated by nicotine [72,73]. As illustrated in Fig. 1, GLP-1 RAs exhibit a broad range of effects on cardiovascular and other systems that are independent of changes in blood glucose. Studies point to cardiovascular protective effects of GLP-1, including an increase in myocardial viability, protection against ischemic and reperfusion injury, increase in the efficiency of energy utilization, improvement of left ventricular function, and favorable effects on serum lipids [74,75]. GLP-1 signaling also suppresses hyperglycemia-induced pro-atherosclerotic factors in vascular endothelial cells, and inflammatory cytokines, including TNF-α and IL-6 [76,77]. Moreover, GLP-1 signaling improves the vascular relaxation response through expression of endothelial nitric oxide synthase activity in endothelial cells [78].

The brain's preproglucagon (PPG) neurons are located in the nucleus tractus solitarius (NTS) and produce brain derived GLP-1 [79–81]. In addition to the hypothalamus and NTS, GLP-1 receptors are expressed throughout the mesolimbic dopamine system, and GLP-1 containing neurons extend directly into the ventral tegmental area (VTA) [82] and nucleus accumbens (NAc) [83,84], which are brain areas critical for reward regulation [71,85,86]. The VTA is a key nucleus that modulates reward behavior and that harbors the cell bodies of dopamine neurons. Activation of GLP-1 receptors in these areas reduces the intake of highly-palatable foods in rodents suggesting that these receptors and the GLP-1 may be involved in stimulation of reward through the mesolimbic dopamine system [71,86], the type of reward that reinforces continued nicotine dependence and smoking.

In addition to this rather direct neuro-stimulatory effect, GLP-1 also mediates satiety through modification of reward signaling, promotion of the sensation of gastric fullness, nausea, and food aversion [87]. Overall, the mesolimbic reward system is a key target not only for food, but also for alcohol, nicotine, and stimulants, and GLP-1 and GLP-1 RA affects the rewarding responses to those substances [88–92]. Because native GLP-1 has a very short circulating half-life of 1–2 min, being degraded by the ubiquitous enzyme, dipeptidyl peptidase IV, pharmaceutical companies have developed longer-

acting GLP-1 analogs such as Exendin-4. Exendine-4 reduces the rewarding effects and decreases the intake of nicotine, cocaine, amphetamine and alcohol in rodents [90,93,94].

4. GLP-1 RAs as potential treatment for TUD and DM comorbidity

As reviewed above, GLP-1 has effects beyond glucose regulation and the GLP-1 system may represent a target for pharmacological treatment of addictive behaviors particularly in patients with DM. Thus, GLP-1 RAs may provide an integrated approach to the treatment of comorbid TUD and DM.

Table 2 lists currently approved GLP-1 RA agents. All of the agents are administered via subcutaneous injection, although an oral formulation of semaglitude is currently being studied to treat DM [95]. Adverse effects differ between specific agents, with the most common being gastrointestinal (GI) related (i.e. nausea, vomiting, and diarrhea) and injection site reactions. Longer acting agents appear to be associated with a lower frequency of GI side effects but higher frequency of injection site reaction [69,96]. Patient satisfaction with both long- and short acting agents is high, and although discontinuation rates due to adverse events vary between agents, the overall discontinuation rate due to adverse events is less than 10% in studies of GLP-1 RAs [69]. In clinical practice the discontinuation rate appears higher [97], possibly because of less time and resources for patient education and follow-up [69]. For example, a retrospective analysis of surveys of real-world multinational practices collecting data from physicians and patients reported that 777 out of 2173 patients with DM (~35%) discontinued GLP-1 RA treatment (used as an add-on therapy) for multiple reasons. The leading reasons were nausea, preference of oral medications over injections, and lack of blood glucose control [98]. The authors attributed this discrepancy to strict exclusion criteria applied for clinical trials, which made the trial data limited for application to the population at large.

GLP-1 RA acting on GLP-1 receptors reduces nicotine intake by several mechanisms related to the location of affected receptors. Stimulation of GLP-1 receptors in the hindbrain NTS can induce [71] nausea, whereas mesolimbic stimulation of GLP-1 neurons affects VTA and NAc with excitatory inputs from the medial habenular (MHb) to the interpeduncular nucleus (IPN) can promote nicotine avoidance. Moreover, the reward-suppressing effects of GLP-1 RAs stimulation can be disassociated from nausea, which is promising for the development of future therapeutics selectively targeting the mesolimbic reward system [71].

Long-acting GLP-1 RAs would likely be more suitable to the treatment of TUD and DM comorbidity due to less frequent

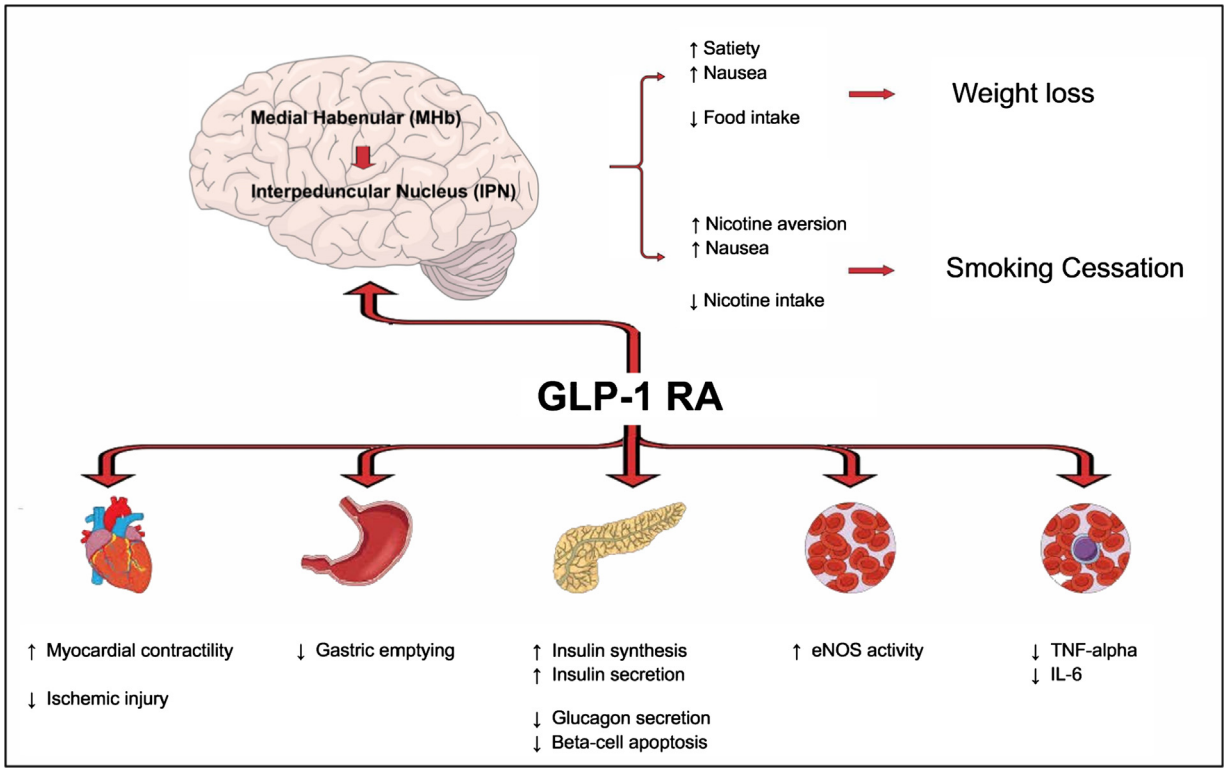

Fig. 1 – Central and peripheral effects of GLP-1 RAs. GLP-1 RAs decrease blood glucose level by stimulating insulin secretion from pancreatic beta-cells (also stimulating their regeneration and preventing apoptosis) and simultaneously suppressing glucagon secretion from alpha-cells. In heart, GLP-1 RAs improve left ventricular function by increasing myocardial viability and contractility and protecting against ischemia and reperfusion injury. GLP-1 RAs also suppress production of inflammatory cytokines (including TNF-α and IL-6) and improve vascular relaxation increasing eNOS activity in endothelial cells. In mesolimbic dopamine system (brain reward regulation center), GLP-1 RAs promote weight loss and smoking cessation by inducing the sensation of gastric fullness, satiety, nausea, as well as food and nicotine aversion.

Table 2 – GLP-1 receptor agonists available in the United States.

Drug	Brand name	Duration of action	Dosing frequency	Delivery device
Exenatide	Byetta®	Short acting	Twice daily	Multiuse pen
Liraglitude	Victoza®	Long acting	Daily	Multiuse pen
Exenatide XR	Bydureon®	Long acting	Weekly	Single-use pen (requires reconstitution)
Lixisenatide	Adlyxin®	Short acting	Daily	Multiuse pen
Dulaglutide	Trulicity®	Long acting	Weekly	Single-use pen
Semaglutide	Ozempic®	Long acting	Weekly	Multiuse pen

dosing with better adherence and their more favorable side effect profiles. The long-acting agents have decreased frequency of nausea and other GI side effects. An ongoing early-phase trial [99] evaluating a potential clinical utility of exenatide XR as a treatment for TUD in pre-diabetic or overweight smokers has a primary outcome of 7-day point prevalence abstinence following 6 weeks of treatment. The results of the study will provide preliminary data for a larger definitive investigation. Notably, over the recent years, several clinical trials have assessed the cardiovascular safety and efficacy of GLP-1RAs, and a recent meta-analysis examined the data from these trials [100]. The findings of this meta-analysis showed cardiovascular safety across all GLP-1 RAs and a potential for reducing the three-point major adverse cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke) and all-cause mortality risk [100]. The cardio-protective potential of the GLP-1RAs would be of particular benefit for DM smokers, a population highly vulnerable to cardiovascular morbidity and mortality.

5. Other glucose-lowering drugs investigated as aids for smoking cessation

Over the recent years, other non-insulin glucose-lowering agents have been explored to aid smoking cessation. Pioglitazone, a peroxisome proliferator-activated receptor agonist, has been shown to alter the abuse potential of addictive drugs (alcohol, opioids, cocaine) in preclinical [101–103] and clinical [104] studies. In a recent report, compared to placebo, pioglitazone was shown to reduce nicotine craving in humans [105].

Lorcaserin, a 5-HT2C agonist, which is currently FDA approved for chronic weight management, but not as a glucose lowering therapy, also decreased nicotine self-administration and nicotine-enhanced responding for conditioned reinforcement in preclinical trials [106–109]. A phase 2 clinical trial reported that compared to placebo, treatment with lorcaserin was associated with a significantly higher continuous abstinence rate and prevention of associated weight gain over a 3-month period [110]. In another phase 2 single-arm trial lorcaserin was combined with varenicline to examine the effects of lorcaserin on the post-cessation weight gain in overweight and obese smokers [111]. The investigators reported decreased weight gain and waist circumference enlargement among participants who achieved prolonged smoking abstinence at 12 weeks [111]. The authors of a recent review on obesity, diabetes, and addiction suggested that lorcaserin could be used as an adjunct therapy for overweight and obese patients to prevent post-cessation weight gain, to improve smoking outcomes and to improve glycemic control in overweight and obese DM patients [112]. Studies of lorcaserin for TUD and DM comorbidity would be helpful to clarify the potential role and mechanism of action for lorcaserin in improving the metabolic and smoking outcomes in DM smokers.

6. Conclusions and future directions

The objective of this review was to discuss the relationship between TUD and DM and to propose a potential new direction for addressing this public health comorbidity. We conclude that GLP-1 RA is a promising set of compounds for the pharmacological treatment of TUD and DM comorbidity.

Future research should examine GLP-1 RAs for TUD and DM comorbidity using a range of outcomes, i.e. efficacy, adherence, and acceptability of GLP-1 RAs as treatment for smoking cessation. Mediating mechanisms by which GLP-RAs may improve smoking outcomes in DM patients are also important. Evaluating glycemic indices and weight would be beneficial, given concerns about worsening glycemic control and weight gain following smoking cessation. GLP-1 RAs can also be combined with the approved smoking cessation therapies (i.e. varenicline) to examine whether GLP-1 RAs improve smoking and other health outcomes beyond those achieved by the currently available treatments in this population.

7. Declarations of interest

None.

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9. Contribution statement

LY conceived the manuscript and wrote the first draft; TK, MP, and JS contributed to the subsequent drafts. All authors have approved the final version of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.033.

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