1

### **Research Article**

# The potential of GLP-1 RAs in treating Tobacco use dependence and Obesity

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Smoking and obesity remain the two most prevalent reversible health risk factors in Singapore. Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1 RAs) are established therapies for diabetes mellitus (DM) and obesity. Recently, they have also shown promise in aiding smoking cessation. Once more robust studies of GLP-1 RAs support this finding, they may play an integral role in reducing the health impact of both risk factors in Singapore.

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# Introduction

Smoking and obesity are both reversible lifestyle factors of public health concern that increase the risk of cardiovascular disease (CVD) and chronic diseases. Despite much effort by the government and the healthcare community, they remain leading contributors to the burden of disease in Singapore. Notwithstanding the multiple measures to curb smoking, crude prevalence of daily smoking in Singapore reported in the National Population Health Survey 2021 was 10.4% (up from 10.1% in 2020) and another 3% are occasional smokers. The smoking prevalence rate in Singapore has been reduced by only a compounded rate of 0.17% per annum for the last 20 years (i.e. 2001 to 2021). Singapore's obesity rate is rising, following a worrying global trend. In the 2020 survey, the incidence of adult obesity was 10.5% whilst a fifth had a high-risk Body Mass Index (BMI). Of the study group, a stark 40% was found to have abdominal obesity, which is associated with a higher risk of CVD. Unsurprisingly, the burden of chronic diseases like DM, hypertension and hyperlipidemia continue to show an increasing trend.<sup>[1]</sup>

To cushion the rising impact of these chronic diseases, the Healthier SG initiative was developed to promote preventative healthcare and health maintenance. Residents identified as having a higher clinical risk are enrolled in structured programs for weight management and smoking cessation under the guidance of healthcare professionals.<sup>[2]</sup>

GLP-1 RAs are commonly used in the treatment of diabetes. Liraglutide, a GLP-1 RA, is also indicated for the treatment of obesity in adolescents and adults in Singapore.<sup>[3]</sup> Preliminary data suggests that GLP-1 RAs may also have utility in aiding smoking cessation. Clinically speaking, GLP-1 RAs have the potential to be used as monotherapy in patients with DM, obesity and tobacco use dependence.

### Methods

A search of PubMed was conducted using key terms such as "GLP-1 agonists", "obesity" and "DM in combination with tobacco use dependence" or "smoking". Relevant peer-reviewed articles published in English were selected for a narrative review.

#### Results

GLP-1 RAs involve mediation of the dopamine dependent neurological reward pathways. These are typically triggered by palatable foods and nicotine consumption. Glucagon-Like-Peptide-1 Receptors (GLP-1R) were identified in reward related areas including the nucleus tractus solitarus (NTS) and nucleus acumbens. In animal studies, GLP-1 RAs have been shown to modulate dopamine levels and glutamatergic neurotransmission resulting in a reduction in both palatable food intake and nicotine use. Likewise in humans, GLP-1 RAs alter palatable food intake and improve activity deficits in the insula, hypothalamus, and orbitofrontal cortex (OFC) through various mechanisms. Upon food consumption, activity in the left insula of diabetic obese patients and activity in the right OFC of obese patients are increased to inhibit overeating. Meanwhile, food cravings are minimised through decreasing the activity in the left insula of diabetic obese patients when food is anticipated.

Exendin 4, a GLP-1 RA, was found to decrease nicotine intake in mice whereas GLP-1R knockout mice increased nicotine intake. [4] Chemogenetic activation of NTS GLP-1 neurons also decreased nicotine intake. Nicotine was found to activate GLP-1 neurons in the NTS. The antidiabetic drugs sitagliptin and exenatide, inhibit GLP-1 breakdown and stimulate GLP-1R, respectively. Both of which decreased nicotine intake in mice. Conversely, GLP-1R knockout mice consumed greater quantities of nicotine

than wild-type mice. GLP-1 excites medial habenular (MHb) projections to the interpeduncular nucleus (IPN). Activation of GLP-1R in the MHb-IPN circuit abolished nicotine reward and decreased nicotine intake, whereas their knockdown or pharmacological blockade increased intake. GLP-1 neurons may therefore serve as 'satiety sensors' for nicotine that stimulate habenular systems to promote nicotine avoidance before its aversive effects are encountered. NTS GLP-1 neurons activated medial habenular projections to the interpeduncular nucleus (IPN), and GLP-1 application into the IPN decreased nicotine intake and attenuated nicotine reward.<sup>[5]</sup>

Two studies evaluated the physiological responses of GLP-1 RAs in patients who smoke. Yannakoulia et al. evaluated the acute effects of smoking and quitting on appetite-related hormones, energy intake and cravings in a randomized cross-over study involving 14 smokers. The participants refrained from food and smoking for 12 hours prior to the study. They were then divided into 2 arms. In the cigarette arm, smokers smoked 2 cigarettes in 15 minutes. In the sham arm, smokers held and puffed their cigarettes without lighting it. After 45 minutes, participants were offered a buffet of snacks. Mean energy intake was significantly less in the cigarette arm compared to the sham arm. More specifically, smokers in the cigarette arm consumed less sweet and salty snacks and less lipids and carbohydrates. Despite this, there were no differences in satiety nor GLP-1 concentrations in both arms. Feeding produced expected changes in ghrelin, cholecystokinin, and insulin levels. Smoking duration was negatively correlated with energy intake. In this study, the changes in food consumption could not be explained by the changes in appetite related hormones. It was proposed that more extensive studies are needed to elucidate the impact of daily cigarette smoking on hormones and appetite.<sup>[6]</sup>

Pankova et al. studied the mechanisms of post cessation weight gain (PCWG) by measuring the effects of smoking cessation on incretin hormones. 13 patients quit smoking and were followed forward. Abstinence was confirmed by carbon monoxide measurement of expired air. Patients had an expected significant increase in body weight and leptin levels (from  $2523 \pm 472$  pg/ml to  $3466 \pm 627$  pg/ml) 3 months after smoking cessation. There was no difference in changes from baseline in any other hormone levels namely gastric inhibitory polypeptide, GLP-1, amylin, insulin, leptin, peptide-YY and pancreatic polypeptide. While the authors acknowledged limitations in their study, they concluded that their findings suggested that incretin hormones are not involved in smoking-related changes in food intake and energy metabolism.<sup>[7]</sup>

Researchers in University Hospital, Basel Switzerland conducted a placebo-controlled, doubleblinded study involving 255 patients evaluating the use of dulaglutide as a novel pharmacotherapy for smoking cessation. There was no significant difference in point-prevalence smoking abstinence rates after 12 weeks between the dulaglutide group (63%) and the placebo group (65%). However, there was a significant (P<0.001) difference in weight with the placebo group gaining 1.8kg (SD 2.4) and the dulaglutide group losing 0.7kg (SD 3.3) between baseline and week 12. The authors concluded that the exceptional high point prevalence abstinence rate in both groups was most probably attributable to the tight supervision of patients. Despite this, GLP-1 RAs such as dulaglutide may still be a promising treatment for smoking cessation as it may avoid PCWG.<sup>[8]</sup>

Similarly, researchers in Texas randomized 84 prediabetic and/or overweight smokers to receive once-weekly exenatide 2mg (a GLP-1 analogue) subcutaneously or placebo. All participants received nicotine replacement therapy and brief smoking cessation counseling. Smoking abstinence evidenced by an expired carbon monoxide level of  $\leq$  5 PPM was evaluated following 6 weeks of treatment. Exenatide was found to increase the chance of smoking abstinence compared to placebo (46.3% and 26.8%, respectively), (risk ratio [RR] = 1.70; 95% credible interval = [0.96, 3.27]; PP = 96.5%). Exenatide also reduced end-of-treatment craving in the overall study group and withdrawal among abstainers. Post-cessation body weight was 5.6 pounds lower in the exenatide group compared to placebo (PP = 97.4%). Adverse events were reported in 9.5% and 2.3% of participants in the exenatide and placebo groups respectively.<sup>[9]</sup>

#### Discussion

Obesity and smoking remain crucial public health concerns in Singapore and are both targets of the Healthier SG initiative. They increase the risk of CVD and chronic diseases; particularly DM. Smoking and DM share a bidirectional relationship. Smoking increases the risk of DM and pre-DM. Compared to smokers without DM, smokers with DM had lower quit rates and displayed greater concern about weight gain following smoking cessation.<sup>[10]</sup>

Diabetics who regularly use tobacco products are twice as likely to experience mortality and negative health outcomes. Their risk of vascular complications is also higher than their non-smoking diabetic counterparts due to the compounded effects of smoking and diabetes. Diabetic smokers are also at an increased risk of central obesity secondary to smoking's anti-estrogenic effects. Obesity further heightens health risk as it impedes glucose control by increasing insulin resistance through multiple factors including excess free fatty acids, increased release of cytokines from adipose tissues and chronic inflammation. Animal studies also demonstrate that disruption of insulin signaling caused by both obesity and DM increases the reward-enhancing effects of nicotine, potentially making smoking cessation more challenging for the patient.<sup>[4,]</sup>

While smoking cessation is undoubtedly associated with positive health outcomes, the period immediately following cessation is linked to weight gain and a deterioration of glycemic control in patients regardless of diabetic status. Study on smokers with DM from a large UK primary care database found a 0.21% increase in HbA1c levels within the first year of quitting.<sup>[11]</sup> In a study funded by the National Institutes of Health, it was reported that the risk of DM was higher among recent quitters, peaking at 5 to 7 years after quitting before gradually decreasing. The increase in DM risk was directly proportional to PCWG.<sup>[12]</sup> Another study from Taiwan echoed similar findings. Smoking cessation was associated with an increased risk of DM and this risk took a minimum of 3 years to attenuate with some variations between studies.<sup>[13]</sup>

In smokers with or without DM, weight gain can be a major adverse effect of smoking cessation, resulting in worsening health conditions. There is a growing body of evidence that nicotine addiction and obesity share common neurobiological pathways. It is therefore not surprising that during smoking abstinence, patients may turn to palatable foods as a substitute, leading to weight gain. This could be a deterrence to quit and may even precipitate a smoking relapse. There is also a substantial risk of obesity and DM associated with PCWG.

To encapsulate, GLP-1 RAs may regulate similar biobehavioral mechanisms that link smoking cessation and overeating. Given the ability of GLP-1 RAs to reduce recreational drug and food intake, it is plausible that targeting GLP-1R signaling may be an effective strategy toward minimising withdrawal-induced weight gain in abstinent smokers. This then lowers the likelihood of DM and obesity whilst potentially increasing the success rate of smoking quit attempts.<sup>[14,]</sup>

## Conclusion

The pre-clinical data on GLP-1 RAs looks promising. Thus far, it has proved to improve smoking cessation rates, attenuate PCWG and reduce the physiological impact of post-cessation glucose derangement along with its recognised efficacy in treating obesity. Therefore, this suggests that GLP-1 RAs may be used as a monotherapy to treat both obesity and nicotine use dependence, with the potential to reduce premature morbidity and mortality from tobacco use and obesity-related diseases, resulting in potential population health, economic and social benefits, such as a reduction in national

health expenditure and overall improvement in national productivity. More comprehensive studies are required to establish GLP1-RA's potential role as a smoking cessation aid.

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