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ORIGINAL ARTICLE

The effect of glucagon-like peptide 1 receptor agonists on alcohol and tobacco craving among patients with type 2 diabetes mellitus: a cross-sectional, questionnaire pilot study

Short title: GLP-1 agonist and alcohol craving

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ABSTRACT

Introduction: Glucagon-like peptide 1 receptor (GLP-1R) agonists are widely used in therapy for type 2 diabetes mellitus (DM2) and obesity. There are also increasing amounts of data concerning the effectiveness of these drugs in the treatment of addictive disorders. This pilot study aimed to assess changes in alcohol-drinking and cigarette-smoking behaviours after the introduction of GLP-1R agonist therapy in patients with DM2.

Methods: Forty-eight (48) patients with obesity and DM2 being treated with GLP-1R agonists completed a questionnaire designed by researchers, the Penn Alcohol Craving Scale (PACS), the Fagerstrom Test for Nicotine Dependence, and the Hunger-Satiety Scale. The severity of alcohol craving and nicotine dependence was compared between one month prior and the week before the evaluation.

Results: Among the 48 patients enrolled on the study, 25 (52%) were treated with liraglutide, 11 (23%) with semaglutide and 12 (25%) with dulaglutide. It was found that changes in PACS total score were statistically significant only in patients treated with semaglutide and that these changes were affected by BMI, marital status, and whether the patient stated that they drank alcohol or smoked cigarettes. Smokers treated with semaglutide had lower Fagerstrom total scores than patients treated with liraglutide.

Conclusion: Semaglutide exerts a reducing effect on alcohol and nicotine craving that was not seen for liraglutide or dulaglutide.

Keywords: GLP-1 receptor agonist, alcohol craving, nicotine craving, questionnaire

Introduction

Gut hormones are new and increasingly widely used incretin-pathway therapeutic agents recommended for use in the treatment of patients with type 2 diabetes mellitus (DM2) and obesity [1, 2]. This group of medicines includes glucagon-like peptide 1 analogues (e.g., exendin-4 [ex-4]) and receptor (GLP-1R) agonists (e.g., liraglutide, semaglutide, dulaglutide, orforglipron, danuglipron, and lixisenatide) and dipeptidyl peptidase-4 inhibitors (DPP-4i), also called gliptins (e.g., sitagliptin, vildagliptin, saxagliptin, and linagliptin). The incretin-based therapy also included partial, dual, and triple agonists, with some examples being orforglipron, a GLP-1R partial agonist; tirzepatide, a GLP-1R and glucose-dependent insulinotropic polypeptide receptor (GIPr) dual agonist; cotadutide, survodutige, and mazdutide, which are glucagon and GLP-1R dual agonists; a combination of cagrilintide (amylin agonist) and semaglutide (GLP-1R agonist) called as CagriSema; combination of GLP-1R and PYY agonists; as well as retatrutide, a triple agonist of GLP-1R, GIP, and glucagon receptors [3–7]. These agents regulate the metabolism of carbohydrates and lipids by increasing insulin and decreasing glucagon secretion, as well as increasing weight loss by slowing gastric emptying and reducing appetite [3]. The use of multi-agonist molecules linking GLP-1R agonists with other gut hormone stimulants may enhance glucagon-mediated appetite suppression, as well as thermogenesis- and lipolysis-promoting effects [6]. An anorexigenic effect of GLP-1R agonists can be modulated by other gut hormones (e.g., orexigenic ghrelin, anorexigenic peptide YY, oxyntomodulin, and cholecystokinin), neuropeptides (e.g., galanin, orexin, and neuropeptide Y), adipocytokines (e.g., adiponectin, leptin, and interleukin-6), the microbiome, short-chain fatty acids, and environmental factors (e.g., meal quality, quantity, and scheduling, and sleep deprivation) [3, 8, 9].

In the light of data revealing the possibility of confusion between alcohol craving and hunger for food [10], appetite reduction via GLP-1R stimulation seems potentially to be effective in the therapy of addictive disorders [11–17]. In obese patients, GLP-1R stimulation was found to reduce alcohol intake [18, 19]; prevent alcohol overuse, alter drinking patterns, suppress alcohol-seeking behaviours, relapse drinking, and the motivation to consume alcohol, and reduce tobacco craving [17, 19–21]; improve gastrointestinal withdrawal symptoms and prevent post-smoking-cessation weight gain (dulaglutide and exenatide); and modulate behavioural and neurochemical responses to addictive drugs (e.g., cocaine and heroin) [11–13, 17, 19–22]. GLP-1R agonists attenuate the direct and indirect influence of alcohol on neurotransmitter secretion (mainly acetylcholine, dopamine, serotonin, noradrenaline, and opioids), mesolimbic dopamine circuit activation, and alcohol reward

regulation; regulate withdrawal-induced anxiety; modulate alcohol-related behaviours; reduce food and fluid intake and appetite; trigger nausea and intestinal discomfort; and alter the taste of alcohol [12, 18]. Similar pathomechanisms also concern addiction to tobacco, including the attenuation of the mesolimbic dopamine system and nicotine-induced rewards [23, 24]. Participation of GLP-1R in the mechanism of addiction to alcohol and nicotine was also confirmed by the prevalence of respective GLP-1R polymorphisms (addiction-like phenotypes) [12] and by a decrease in GLP-1R expression after intravenous alcohol or cocaine infusion. These anti-addictive effects of GLP-1R agonists on addiction-related outcomes were observed after treatment for both acute and chronic use.

It should be underlined that GLP-1R agonists also exert more recognizable favourable effects that can provide an additional benefit of alcohol- and tobacco-dependence treatment. These effects include body weight reduction, improvement in obesity-related disorders and carbohydrate metabolism, reduction in endothelial dysfunction and chronic inflammation, regulation of the renin-angiotensin system, and other cardioprotective properties that lead to an evidenced reduction in cardiovascular morbidity (e.g., myocardial infarction and heart failure with preserved ejection fraction) and mortality [1, 2, 25]. Through the cardioprotective and metabolic GLP-1R agonist actions mentioned, existing alcohol use disorders and smoking-related organ injury, especially to the cardiovascular system), can potentially be reversed [1, 2, 17].

In light of the data referred to above, the authors are attracted by the hypothesis that GLP-1R agonists could be therapeutic agents for reducing alcohol drinking and cigarette smoking, preventing alcohol- and smoking-related disorders and drinking relapse and maintaining alcohol drinking and cigarette smoking abstinence. However, to date, the data concerning GLP-1R anti-addictive effects originate mainly from studies performed in animals (e.g., rats, mice, and monkeys) [12–16, 21], and only a few studies on GLP-1R use in addictive disorders have been performed in humans. Therefore, this questionnaire-based pilot study was performed to assess changes in alcohol-drinking and cigarette smoking behaviours after the introduction of GLP-1R agonist therapy in patients with DM2.

Patients and methods

Patients

Forty-eight patients (women and men) with DM2 and obesity treated with GLP-1R agonist were enrolled on the study in a diabetic outpatient clinic.

Methods

The patients completed researcher-designed and standard questionnaires that included socio-demographic and clinical information. Patients answered the questions in relation to two measurement points: their current status (i.e., in the week up to the evaluation point) and their status four weeks earlier.

- Researcher-designed questionnaire: this questionnaire assesses appetite for food, alcohol craving, and nicotine urges in the range from –5 (“very strongly do not experience”) to +5 (“very strongly experience”).
- Hunger-Satiety Scale: the scale assesses the intensity of hunger and satiety in the range from 0 (“starving, no energy, very weak”) to 10 (“extremely stuffed, nauseous”) [26].
- Penn Alcohol Craving Scale (PACS): a five-item questionnaire adapted by Chodkiewicz et al. [27] to assess the intensity, frequency, and course of alcohol craving, the risk of relapse when drinking is possible, and the intensity of overall craving over the previous seven days. The questionnaire has appropriate psychometric properties and is often used in studies of alcohol craving. The higher the total scale score, the more intense the alcohol craving.
- Fagerstrom Test for Nicotine Dependence: a six-item standard instrument that assesses the intensity of physical nicotine dependence. The outcomes are summed to yield a total score of between 0 and 10. The higher the total scale score, the more intense the physical dependence on nicotine [28].

Bioethics

The investigation was conducted in compliance with the Declaration of Helsinki for medical research with the permission of the local Bioethical Committee (KB No. 180/2021).

Statistics

Statistical analysis was conducted using the licensed version of the statistical software Statistica, version 13.3, developed by Tibco Software, Inc. (2017). The normal distribution of the study variables was checked using the Kolmogorov-Smirnov test. The results are presented as the mean ± standard deviation, or n, %. Statistical significance of differences between groups was assessed using the ANOVA method with one and two repetitions and post-hoc tests, or with a Chi^2 test.

Results

Among the 48 patients enrolled on the study, 25 (52%) were treated with liraglutide, 11 (23%) with semaglutide, and 12 (25%) with dulaglutide (Tab. 1). The respective patient groups treated with the various GLP-1R agonists differed with regard to age, body mass index (BMI), whether the patient stated that they consumed alcohol, and scoring in the first question of the PACS survey (Tab. 1). There were no further statistically significant differences in alcohol craving, nor any differences in hunger intensity or tobacco craving, either in the week of the evaluation or one month earlier, between the respective study groups.

Next part of the analysis compared the influence of clinical factors on changes in PACS total score one month and in the survey was completed between the respective GLP-1R agonists (Tab. 1). It was found that changes in PACS or and Fagerstrom survey total scores were statistically significant only in patients treated with semaglutide and that these were affected by: (a) BMI group (the main effect was that in patients with overweight (BMI value between 25 and 30 kg/m^2), the PACS total score was higher than in patients with a BMI > 30 kg/m^2 (obesity) during the period analysed) (Fig. 1A); or (b) marital status (of those who were single, married, divorced, or widowed, PACS total score was the highest in divorced patients) (Fig. 1B); and (c) drank alcohol or smoked cigarettes (PACS total score was higher in smokers and alcohol drinkers than in their counterparts) (Fig. 1C). No statistically significant effect was found of clinical factors and treatment with a GLP-1R agonist on scores in the Fagerstrom survey in whole study group.

Next, the analysis was repeated only among patients who had declared an alcohol-drinking (n = 18) or smoking (n = 5) habit. Among smokers, a statistically significant main effect of semaglutide on Fagerstrom survey total scores (Fig. 1D) was found. Whereas, in patients who declared that they drank alcohol, a statistically significant effect of semaglutide treatment on the score given for the third question in the PACS questionnaire (“During the past week how much time have you spent thinking about drinking or about how good a drink would make you feel?”): the score for the week the survey was completed was significantly lower than the score for one month before (Tab. 1, Fig. 1C). No statistically significant influence of GLP-1R agonist treatment on hunger and satiety score either before or after a meal was found.

Discussion

It was revealed that only semaglutide exerts a statistically significant effect on alcohol (a decreased PACS score for the third question) and tobacco (a lower Fagerstrom total score in

patients treated with semaglutide compared with those treated with liraglutide) craving, both in the whole study group and in patients who declared that they used these substances (Tab. 1; Fig. 1C and 1D). The effect of GLP-1R agonists in decreasing PACS (third question) was affected by BMI group and marital status. Overweight and divorced patients had higher PACS total scores than patients with a BMI > 30 kg/m^2 (Fig. 1A) and individuals with another marital status (Fig. 1B), respectively. PACS total score was higher in smokers and alcohol drinkers than in their counterparts (data not shown).

The data obtained corroborate the results of other studies. It was previously reported that BMI may be a predictor of alcohol drinking relapse and readmission for addiction treatment [29], although the research did find a higher PACS total score in overweight patients than in those who were obese (Fig. 1A). Acute psychosocial stress, associated with, for example, living alone, also induced more craving and correlated with the risk of alcohol drinking [30], which in this study was expressed as a higher PACS total score for divorced patients (Figure 1B). The present observations were also consistent with data cited in the Introduction section that revealed both in rats and humans a lowering effect of GLP-1R agonists on appetite, and on alcohol and nicotine craving [11–25, 31], which was the strongest in the present study in patients treated with semaglutide [32], both with regard to alcohol drinking (Fig. 1C) and tobacco smoking (Fig. 1D). It was also reported that exenatide in combination with nicotine replacement therapy improved smoking abstinence, reduced craving and withdrawal symptoms, and decreased weight gain among abstainers [14], whereas 12-week subcutaneous dulaglutide with standard smoking cessation therapy (varenicline 2 mg/day and behavioural counselling) did not improve smoking abstinence when compared to a placebo, and a preventive effect against weight gain after smoking cessation disappeared after stopping GLP-1R agonist treatment [24]. Moreover, liraglutide and ex-4 attenuated nicotine self-administration, withdrawal-induced hyperphagia, and weight gain in male and female rats and mice [21, 23]; however, in the present study, the liraglutide effect on the severity of nicotine dependence score was less than for semaglutide (Fig. 1D). The present results also confirmed known crossover associations of alcohol and smoking craving, which were observed in the present study as a lowering effect of semaglutide on alcohol craving and severity of nicotine dependence (Fig. 1C and 1D) [32–34]. Moreover, the obtained results were also consistent with a recently published retrospective cohort study by Wang et al. [35], which was based on electronic health records of 83,825 patients with obesity and revealed that semaglutide was associated with a 50–56% lower risk of both the incidence and recurrence of alcohol use disorder in a 12-month follow-up period when compared to other anti-obesity medications.

Study limitations

This study should be treated as preliminary due to several limitations, related mainly to its questionnaire-based methodology, cross-sectional and retrospective design, small sample size, and, further, the low proportion of patients who declared that they drank alcohol or smoked cigarettes. Moreover, it did not assess the quantity of alcohol drunk, or the number of cigarettes smoked.

Conclusion

Semaglutide exerts an effect in reducing alcohol and nicotine cravings that was not seen for liraglutide or dulaglutide. Further studies are needed to explore the effect of semaglutide in potentially reducing alcohol and nicotine use disorders and the cardiovascular risk for patients with DM2 and obesity.

Article information

Data availability statement: *Data are available.*

Ethics statement: *The investigation was conducted in compliance with the Declaration of Helsinki for medical research with the permission of the local Bioethical Committee (KB No. 180/2021).*

Authors contribution: *Study Design: Jacek Budzyński, Marcin Ziółkowski, Damian Czarnecki; Data Collection: Damian Czarnecki, Marcin Kruszewski, Anna Długosz; Statistical Analysis: Jacek Budzyński, Marcin Ziółkowski, Damian Czarnecki; Data Interpretation: Beata Czerniak, Wioletta Banaś, Jacek Budzyński; Manuscript Preparation: Jacek Budzyński, Marcin Ziółkowski, Damian Czarnecki; Literature Search: Jacek Budzyński, Damian Czarnecki, Marcin Kruszewski, Anna Długosz; Approval of final manuscript version: Jacek Budzyński, Damian Czarnecki, Marcin Kruszewski, Anna Długosz, Marcin Ziółkowski*

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Table 1. Clinical characteristics of the patients studied

Characteristic	**Liraglutide (L) (n = 25)**	**Semaglutide (S) (n = 11)**	**Dulaglutide (D) (n = 12)**	**p L:S**	**p L:D**	**p S:D**
Male gender (n, %)	14 (56.0)	8 (72.7)	7 (58.3)	0.357	0.897	0.492
Age (years)	57.36 ± 11.87	49.45 ± 13.81	66.00 ± 7.69	0.089	0.028	0.002
Body weight (kg)	94.29 ± 19.04	103.55 ± 13.81	100.69 ± 1.99	0.178	0.295	0.650
Height (cm)	171.04 ± 9.97	168.36 ± 17.47	168.25 ± 8.73	0.460	0.416	0.976
BMI (kg/m^2)	31.91 ± 3.99	36.47 ± 4.22	35.87 ± 5.66	0.004	0.020	0.776
Number of comorbidities	1.52 ± 1.45	1.00 ± 0.77	1.92 ± 1.24	0.272	0.420	0.048
Smoking habit (n, %)	3 (12.0)	2 (18.2)	0	0.633	0.222	0.134
Alcohol drinking (n, %)	14 (56.0)	2 (18.2)	2 (16.7)	0.036	0.024	0.928
Food hunger severity (score)	0.12 ± 1.99	–0.36 ± 2.38	–0.25 ± 2.30	0.530	0.617	0.908
Tobacco craving severity (score)	0.08 ± 1.04	–0.36 ± 1.29	–0.42 ± 1.44	0.280	0.239	0.927
Alcohol craving severity (score)	–0.04 ± 1.31	0.09 ± 0.30	–0.42 ± 1.44	0.746	0.433	0.266
Pre-meal hunger severity (current)	3.86 ± 0.65	4.09 ± 0.83	4.20 ± 0.42	0.389	0.143	0.713
Pre-meal hunger severity (one month before)	6.66 ± 1.08	7.09 ± 0.94	6.50 ± 1.20	0.270	0.732	0.244
Post-meal hunger severity (current)	2.90 ± 1.00	3.00 ± 1.00	3.44 ± 0.73	0.799	0.155	0.281

Post-meal hunger severity (one month before)	7.31 ± 1.25	7.36 ± 1.86	7.00 ± 1.69	0.922	0.593	0.668
D-pre-meal hunger	0.95 ± 0.97	1.09 ± 0.83	0.78 ± 0.97	0.691	0.655	0.447
D-post-meal hunger	–0.52 ± 0.98	–0.27 ± 1.27	–0.42 ± 1.90	0.539	0.863	0.837
PACS total score (current)	1.40 ± 2.48	0.45 ± 1.21	0.00 ± 0.00	0.241	0.061	0.208
PACS1	0.48 ± 0.65	0.09 ± 0.30	0.00 ± 0.00	0.069	0.016	0.307
PACS2	0.28 ± 0.61	0.18 ± 0.40	0.00 ± 0.00	0.631	0.126	0.134
PACS3	0.16 ± 0.37	0.00 ± 0.00	0.00 ± 0.00	0.169	0.150	
PACS4	0.12 ± 0.44	0.00 ± 0.00	0.00 ± 0.00	0.376	0.354	
PACS5	0.36 ± 0.65	0.18 ± 0.60	0.00 ± 0.00	0.438	0.060	0.307
PACS total score (one month before evaluation)	1.44 ± 2.53	0.36 ± 1.21	0.00 ± 0.00	0.191	0.059	0.307
PACS1-1	0.52 ± 0.71	0.09 ± 0.30	0.00 ± 0.00	0.065	0.017	0.307
PACS2-1	0.28 ± 0.68	0.00 ± 0.00	0.00 ± 0.00	0.183	0.165	
PACS3-1	0.20 ± 0.41	0.09 ± 0.30*	0.00 ± 0.00	0.433	0.101	0.307
PACS4-1	0.12 ± 0.44	0.00 ± 0.00	0.00 ± 0.00	0.376	0.354	
PACS5-1	0.36 ± 0.70	0.18 ± 0.60	0.00 ± 0.00	0.469	0.086	0.307
Fagerstrom scale score (current)	0.92 ± 2.50	0.73 ± 1.62	0.00 ± 0.00	0.816	0.214	0.134
Fagerstrom scale score (one month before evaluation)	0.92 ± 2.50	0.73 ± 1.62	0.00 ± 0.00	0.816	0.214	0.134
D-PACS total score	0.04 ± 0.93	–0.09 ± 0.30	0.00 ± 0.00	0.655	0.884	0.307
D-PACS1	0.04 ± 0.20	0.00 ± 0.00	0.00 ± 0.00	0.515	0.496	
D-PACS2	–0.00 ± 0.41	–0.18 ± 0.40	0.00 ± 0.00	0.226	1.000	0.134
D-PACS3	0.04 ± 0.20	0.09 ± 0.30	0.00 ± 0.00	0.552	0.496	0.307
D-PACS4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00			
D-PACS5	–0.00 ± 0.29	0.00 ± 0.00	0.00 ± 0.00	1.000	1.000	
D-Fagerstrom total score	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00			

BMI — body mass index; D — delta, which is the difference between the survey score one month before and in the week of the evaluation; Fagerstrom — Fagerstrom Test for Nicotine Dependence questionnaire; PACS — Penn Alcohol Craving Scale; * — $p < 0.05$ between measurements at one month before and in the week of the evaluation

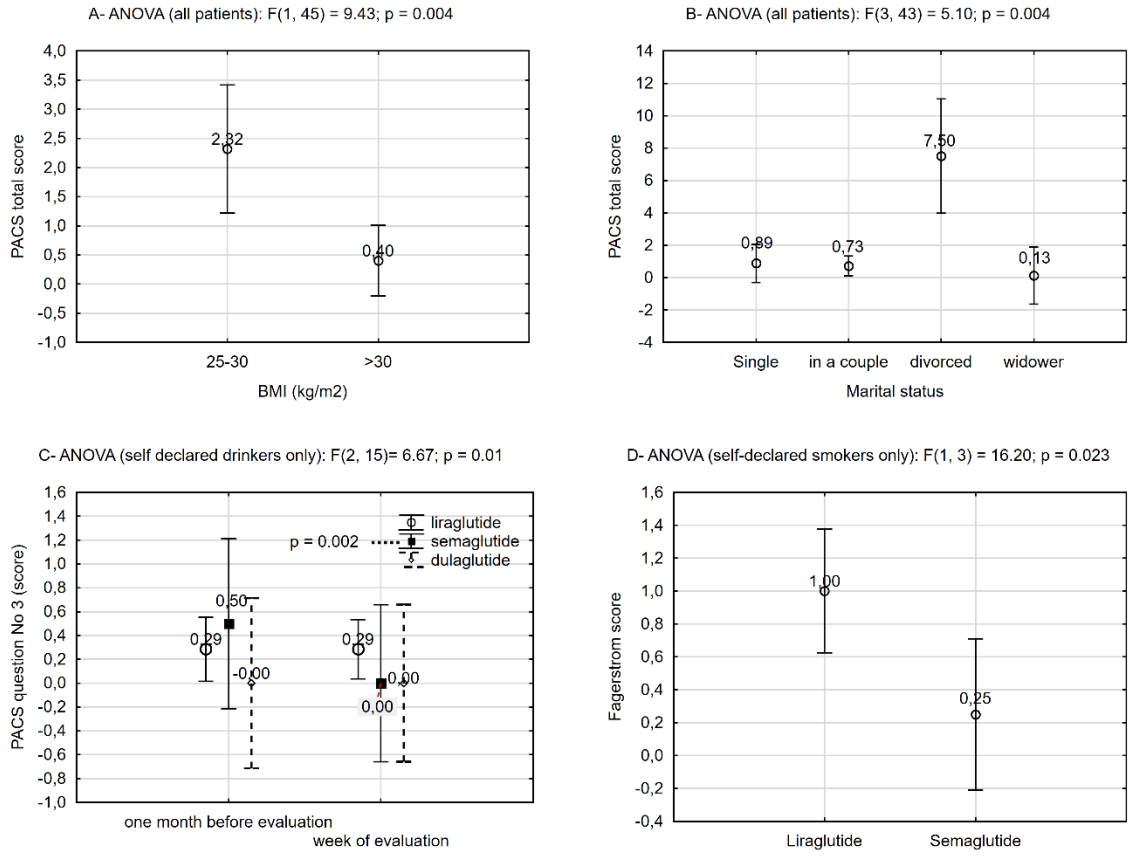

Figure 1. PACS score (A–C) and Fagerstrom score (D) in relation to BMI range, marital status, and type of GLP-1R agonist treatment (C–D). Two-way repeated measures ANOVA