European Review for Medical and Pharmacological Sciences 2023; 27: 3545-3551

Intragastric injection botulinum toxin A for obesity management with or without liraglutide

Ç. ALTUNAL[1], I.T. SAHINER[2], S. YAVUZER[3], M. CENGIZ[3], T. SADIKOĞLU[4]

[1]Department of Perfusion Techniques, School of Medicine, Nişantaşı University, Istanbul, Turkey
[2]Department of General Surgery, Hitit University School of Medicine, Corum, Turkey
[3]Department of Internal Medicine, School of Medicine, Aydin University, Istanbul, Turkey
[4]Department of Medical Education, School of Medicine, Biruni University, Istanbul, Turkey

Abstract. – OBJECTIVE: Obesity is a global public health problem with rapidly increasing prevalence in many countries, including Turkey, and different treatment modalities have been used. This study aimed to compare the effect of intragastric botulinum toxin A (BTA) injection and BTA injection combined with low-dose liraglutide in patients with obesity.

PATIENTS AND METHODS: Records of 701 patients (female/male, 660:41; mean age, 45.6 ± 6.2 years) who received an intragastric injection of BTA for weight loss between November 2019 and May 2020 were reviewed retrospectively. The patients were divided into the BTA group, which included patients who received BTA injection alone, and BTA + liraglutide, which included those who used liraglutide after BTA injection. The demographic characteristics and comorbid diseases of the patients and follow-up results 6 months after the procedure were evaluated.

RESULTS: In the comparison of the 3-month and 6-month weights of the patients, weight measurements were significantly lower in the BTA + liraglutide group than in the BTA group ($p < 0.001$ and $p < 0.001$, respectively). Adverse effects were observed in 212 (30.2%) of the study participants, of which 25% were observed in the BTA group and 31.8% in the BTA + liraglutide group, with no significant difference.

CONCLUSIONS: The intragastric injection of BTA combined with liraglutide is a safe method that provides more effective weight loss than BTA alone, which is minimally invasive without any serious adverse effects.

Key Words:
Obesity, Botulinum toxin type A, Liraglutide, Gastroscopy.

Introduction

Obesity is globally endemic, and its prevalence has been increasing rapidly worldwide. According to the World Health Organization, it is the epidemic of the century. In 2016, 650 million adults had obesity globally, and it has doubled since 1980[1,2]. In the study of conducted in Turkey, Diabetes, Hypertension, Obesity, and Endocrinological Diseases Prevalence Study II (TURDEP II), two-thirds of the adult population are overweight or have obesity[3]. Obesity is an important disease that increases the risk of cardiovascular problems and deaths from all other causes. Additionally, it is an important risk factor that increases the frequency of hypertension, dyslipidemia, type 2 diabetes mellitus (DM), stroke, gallbladder diseases, osteoarthritis, sleep apnea syndrome, and some cancer types. Obesity and the diseases it causes have not only biological but also psychosocial and economic effects on human and social life. Patients with obesity are associated with 30% more hospital admissions, 50% more hospitalizations, and 80% more drug costs than the population of normal weight. In the USA, health expenditures related to obesity are approximately 190 billion annually[4]. As a result, the prevention and treatment of obesity are not only a public health issue but also a socioeconomic problem.

The treatment of obesity is mainly based on lifestyle management, dietary counseling, psychiatric consultation, and exercise. However, with the rapid increase in incidence, various treatment options have been made available in the last 10 years, such as pharmacotherapy (orlistat, glucagon-like peptide-I analog), bariatric surgery, gastric balloon, and intragastric injection of botulinum toxin A (BTA)[1,5]. According to these data, it is very important to prevent and treat obesity, which is one of the serious global health problems. Surgical treatment options possess some disadvantages, such as anatomical changes, complication risks, and longer postoperative hospital stay. Therefore, it is very important to find other interventional treatment methods that do not require further medical treatment or hospitaliza-

Corresponding Author: İbrahim Tayfun Şahiner, MD; e-mail: tayfunsahiner@gmail.com

tion. Moreover, there is a huge need to investigate the effectiveness of these new methods, which will contribute to the prevention and treatment of obesity.

This study aimed to compare the effect of intragastric botulinum toxin A (BTA) application with dietary changes and the use of BTA with low-dose liraglutide [glucagon-like peptide (GLP-1) agonist] in patients with obesity.

Patients and Methods

Study Design and Sampling

Records of patients followed up by a dietitian at the outpatient clinics of Internal Medicine and General Surgery between November 2019 and May 2020 were reviewed retrospectively. These records included 160 patients who underwent intragastric BTA injection in addition to diet and 541 patients who were started on low dose liraglutide after intragastric BTA injection in addition to diet. In total, 701 patients (female/male, 660:41; mean age, 45.6 ± 6.2 years) who met the inclusion criteria were included in the study.

Selection Criteria

Patients in both groups were evaluated by the same dietitian and given a similar low-calorie medical diet that was appropriate for their comorbidities. Pen training of the patients who started liraglutide was provided by the same diabetes nurse. While the patients continued their dietary programs, they were treated by the same physician with either an intragastric BTA injection alone (BTA group) or an intragastric BTA injection with low dose liraglutide therapy (BTA + liraglutide group). The age, sex, weight, body mass index (BMI), comorbid diseases of the patients, and the follow-up results at 6 months after the interventions were evaluated.

Patients aged 18-60 years with or without any comorbidities and BMI > 30 kg/m^2 were included in the study. Patients who presented with the following criteria were excluded: endocrine-related obesity; recent (< 3 months) anti-obesity treatment, including GLP-1 analogs; active gastrointestinal disease (endoscopy-diagnosed esophagitis, peptic ulcer, cancer, etc.) or history of gastric surgery; gastrointestinal motility dysfunction caused by opioid treatment, anticholinergics, or other drugs; history of intolerance to liraglutide therapy or withdrawal of the therapy in 6 months; and pregnancy or breastfeeding.

Endoscopy

An upper gastrointestinal tract endoscopy was performed on all patients. For the gastric BTA injection, 500 U abobotulinumtoxinA (Dysport®; Ipsen Biopharm Ltd, Wrexham, UK) was diluted in 25 mL of physiological saline solution. Then, 1 mL of this solution was injected into 25 points of the stomach muscle layer using an endoscopic needle. Injections were performed in a circular distribution: five injections were performed in circles at a distance of 3, 5, 7, and 9 cm from the pyloric ring with equal distance in a fifth circle at the fundus level.

Patient Follow-up

Each patient was scheduled for three visits: after the endoscopy, at 3 months, and at 6 months. Physical examination was performed in all visits with the assessment of weight, height, and BMI. With the patients not wearing clothes and shoes, weight and height were measured using an electronic scale (SECA 665, Hamburg, Germany). At each follow-up visit, the patients were asked about any adverse effects.

Dosage and Administration of Liraglutide

A prefilled, multi-dose 6 mg/mL liraglutide pen (Saxenda, Novo Nordisk®, Bagsværd, Denmark) that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg (6 mg/mL, 3 mL) was used in the BTA + liraglutide group, which was administered subcutaneously once a day independent of meals. Patients were trained for the injection in different body sites, such as the abdomen, thigh, or upper arm. The application started with 0.6 mg/day, and the dosage was increased to 1.2 mg/day 1 week later. Liraglutide treatment was continued for 6 months for all patients at the same dosage.

Statistical Analysis

Data that fit into a normal distribution were analyzed by the Kolmogorov-Smirnov test. Categorical variables are presented as percentages, whereas continuous variables are presented as mean ± standard deviation. Categorical variables were analyzed using the Chi-square test, whereas continuous variables in two-way groups were analyzed using the *t*-test. All data were tested by using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), and values of $p < 0.05$ were considered significant.

Results

The demographic characteristics and comorbidities in the studied groups are shown in Table I. No remarkable difference was found between the two groups regarding age, sex distribution, smoking status, and comorbidities.

Changes in weight and BMI at the 6-month follow-up are presented in Table II. In the BTA group, the initial weight was 97.8 ± 23.3 kg (BMI, 36.7 ± 4.7 kg/m^2), whereas in the BTA + liraglutide group, it was 100.1 ± 23.9 kg (BMI, 36.8 ± 4.9 kg/m^2), with no difference between the groups. When the 3-month and 6-month weights were compared, the weight was significantly lower in the BTA + liraglutide II than in the BTA group ($p < 0.001$ and $p < 0.001$, respectively) (Figure 1). The mean weight loss in the first 3 and 6 months was 7.6 ± 2.7 kg and 9.8 ± 4.5 kg in the BTA group, whereas it was 16.8 ± 5.1 kg and 24.9 ± 8.2 in the BTA + liraglutide group, respectively, which was also significant ($p < 0.001$) (Figure 2).

The summary of safety data and adverse effects on the study population are shown in Table III. Side effects were observed in 212 (30.2%) of all study participants, of which 25% were observed in the BTA group and 31.8% in the BTA + liraglutide group, with no remarkable difference. The side effects and the number and percentage of the patients were as follows: nausea 66 (9.4%), vomiting 49 (7%), abdominal pain 12 (1.7%), flatulence 55 (7.8%), diarrhea 7 (1%), and constipation 66 (9.4%). No patients had serious side effects, including hypoglycemia or severe hypoglycemia.

Table I. Demographic characteristics and comorbidities of the study population.

	Group I (BTA) (n=160)	Group II (BTA+ Liraglutide) (n=541)	p
8 Age (years)	45.8 ± 5.9	45.5 ± 6.2	0.598
Gender (female)	150 (93.8)	510 (94.3)	0.848
Smoking	47 (29.4)	155 (28.7)	0.671
Comorbidities			
Hypertension	60 (37.5)	208 (38.5)	0.854
Diabetes mellitus	33 (20.6)	115 (21.3)	0.913
Hyperlipidemia	30 (18.8)	99 (18.3)	0.908
CVD	7 (4.4)	27 (4.9)	0.837
OSAS	13 (8.1)	39 (7.2)	0.731
PCOS	5 (3.1)	21 (3.8)	0.814

BTA, botulinum toxin A; CVD, cardiovascular disease; OSAS, obstructive sleep apnea syndrome; PCOS, polycystic ovarian syndrome.

Table II. Changes in the weight and BMI in 6-month follow-up of the study population.

	Group I (BTA) (n=160)	Group II (BTA+ Liraglutide) (n=541)	p
0-month weight (kg)	97.8 ± 23.3	100.1 ± 23.9	0.301
0-month BMI (kg/m^2)	36.7 ± 4.7	36.8 ± 4.9	0.830
3-month weight (kg)	90.2 ± 21.2	83.3 ± 19.8	**<0.001**
3-month BMI (kg/m^2)	33.9 ± 4.4	30.6 ± 4.3	**<0.001**
The change of weight between 0-3 months	-7.6 ± 2.7	-16.8 ± 5.1	**<0.001**
6-month weight (kg)	88.1 ± 20.6	75.1 ± 17.9	**<0.001**
6-month BMI (kg/m^2)	32.9 ± 4.3	27.6 ± 3.9	**<0.001**
The change of weight between 0-6 months	-9.8 ± 4.5	-24.9 ± 8.2	**<0.001**

BMI, body mass index; BTA, botulinum toxin A.

Discussion

This study demonstrated that patients who received intragastric BTA injection and liraglutide lost more weight at the 3-month and 6-month follow-up than patients who only received BTA injection. No significant difference was found between those patients with respect to adverse effects.

To prevent obesity globally, there is a huge need for the use of more cost-effective methods with lower side effects than bariatric surgery and shorter hospitalization time, combined with pharmacotherapy and lifestyle changes[6,7]. Current guidelines recommend lifestyle and dietary changes as a priority in the struggle to lose excessive weight[8]. However, in case of failure, bariatric surgery is still accepted as the gold standard treatment, especially for patients with class III (BMI > 40 kg/m^2) and class II (BMI 35-40 kg/m^2) obesity with obesity-related comorbidities[9]; however, there is no consensus about the weight loss of patients with class I (BMI 30-35 kg/m^2) and class

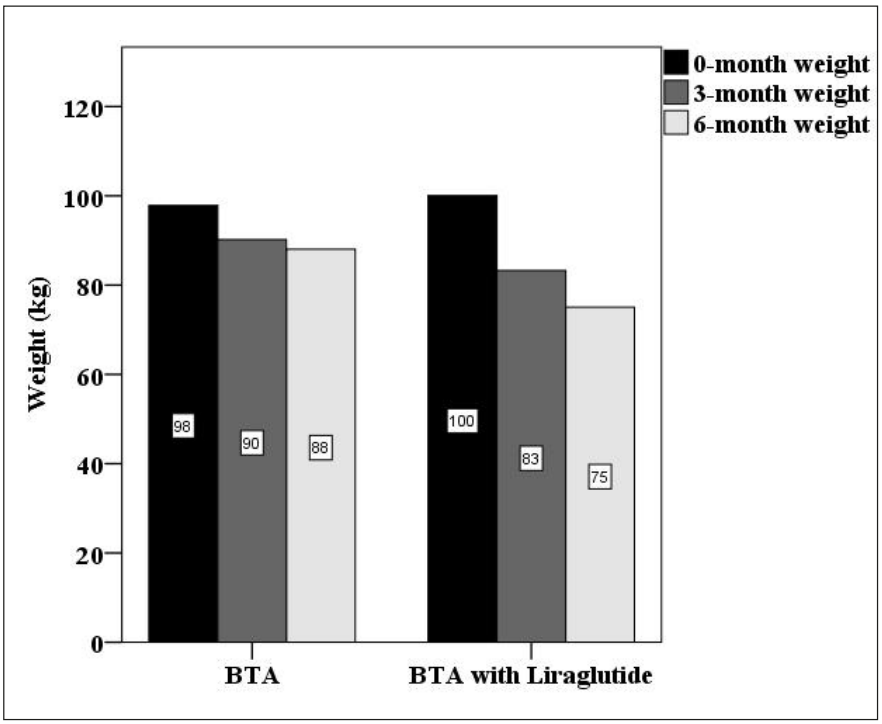

Figure 1. Body weight averages of the groups at 0, 3, and 6 months.

II obesity with obesity and healthy patients. Such patients benefit from minimally invasive treatments such as endoscopic methods[10]. Since the current guidelines still recommend lifestyle and dietary changes as the initial treatment, supportive alternative methods will help patients with this condition, which will make it easier to follow their diet and decrease the need for surgery.

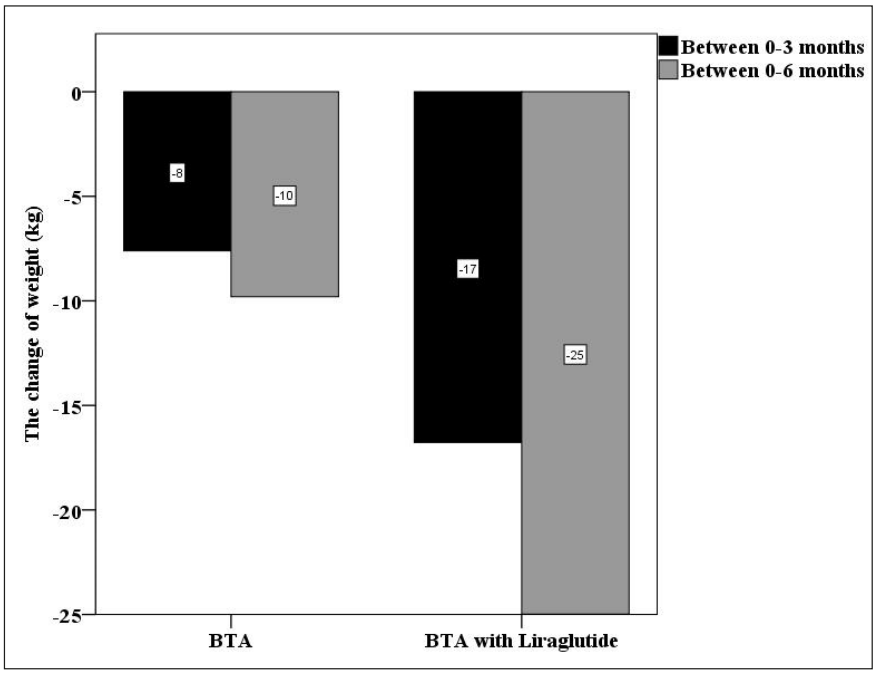

Figure 2. Average of changes in body weights of the groups between 0-3 months and between 0-6 months.

Table III. Demographic characteristics and comorbidities of the study population.

	Group I (BTA) (n=160)	Group II (BTA+ Liraglutide) (n=541)	p
Participants with any AEs	40 (25)	172 (31.8)	0.117
Nausea	10 (6.3)	56 (10.4)	0.126
Vomiting	8 (5)	41 (7.6)	0.295
Abdominal pain	2 (1.3)	10 (1.8)	0.608
Flatulence	10 (6.3)	45 (8.3)	0.503
Diarrhea	3 (1.9)	4 (0.7)	0.199
Constipation	13 (8.1)	53 (9.8)	0.644
Hypoglycemia	0	0	
Severe hypoglycemia	0	0	

AE, adverse effects; BTA, botulinum toxin A.

BTA is a neurotoxic protein produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium.

Eight serotypes are known and identified as serotypes A, B, C1, C2, D, E, F, and G. BTA inhibits the release of acetylcholine at the neuromuscular junction, preventing the contraction of smooth and striated muscles. BTA has been used in clinical practice for many years to treat inappropriate and long-term muscle contractions[11].

Studies[12,13] have shown positive results with BTA application in the treatment of diffuse esophageal spasms, achalasia, oropharyngeal dysphagia, anismus, anal fissures, and rectocele. The injection of BTA into the gastric wall is a newly developed endoscopic treatment for obesity. The toxin inhibits the release of acetylcholine in cholinergic neuromuscular junctions.

BTA delays gastric emptying and leads to early satiety by acetylcholine-mediated inhibition of gastric antral motility[14]. The effect gradually disappears in 3-6 months and does not cause permanent damage[11]. The most attractive feature of BTA treatment is the absence of serious adverse effects and procedural complications regardless of the technique, dose, or injection site[15-17]. In a randomized, double-blind, placebo-controlled study by Sánchez et al[18], 52 patients with obesity who underwent BTA were followed up for 24 weeks and lost an average of 4.6 kg, whereas in our study, the BTA group lost approximately 9.8 kg at the 6- month follow-up.

GLP-1 is secreted from the L cells of the distal intestinal mucosa following food intake. GLP-1 dipeptidyl peptidase-IV enzyme (DPP-IV) causes GLP-1 to lose its effect in less than 2 min, which limits its action[19]. Some studies[20] have revealed that many GLP-1 analogs resistant to DPP-IV have been developed. Liraglutide has 97% structural homology with human GLP-1 with a half-life of 10-14 h. In 2010, the daily use of 1.8 mg liraglutide was approved by the Food and Drug Administration for the management of type 2 DM[21]. Many clinical studies[22] have shown the effects of GLP-1 analogs on weight loss. Liraglutide delays gastric emptying, but this effect decreased significantly following long-term (14 days) treatment. Therefore, the delay only on gastric emptying does not contribute significantly to weight loss[23]. Neuroanatomical and behavioral evidence has shown that GLP-1 analogs probably reduce the intake of high-fat and sugary foods by reducing their flavors[24]. In a meta-analysis, Zhang et al[25] included 4,754 patients without DM but having obesity and using liraglutide and observed 6-8.4 kg of weight loss in their follow-up at 14-56 weeks. In our study, patients who used BTA with liraglutide lost approximately 24.9 kg at the 6-month follow-up and lost more weight than patients who received BTA alone.

A study in rats showed that the combination of low doses of leptin and liraglutide provides greater weight loss than its single use[26]. In addition, combined therapy in obese rats treated with liraglutide and melanocortin-4 receptor agonist provided greater weight loss and better glycemic control with enhanced cholesterol metabolism[27]. Similar to our study, in the literature has been shown that combined therapies are more effective than single-use liraglutide. Thus, the 6-month cost of liraglutide treatment, which is higher for countries with low purchasing power, can be lowered by BTA combination, and a synergistic effect can be created with the combination. According to these findings, combined therapies and appropriate nutrition protocols can be much more effective in the achievement of fewer side effects, lower costs, and better results.

Limitations

This study has some limitations. First, the results of this study cannot be generalized to the general population because of its cross-sectional design, single-center setting, and non-inclusion of patients aged < 18 and >60 years. Second, it cannot provide long-term weight changes because the follow-up lasted only for 6 months. Finally, the majority of our patients were female; thus, studies with a greater number of both sexes are needed.

Conclusions

Compared with a single BTA injection, intragastric injection of BTA combined with liraglutide is a safe method that provides a more effective weight control in patients, is minimally invasive, and had no serious side effects. Further studies are needed to clarify the mechanisms related to patients' responses and their advantages in clinical practice.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest
The authors declared no conflict of interest.

Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

Ethics Approval
Formal consent Ethical approve was obtained from Biruni University (Date: November 7, Number 2019/3404).

Informed Consent
Not applicable due to the retrospective nature of the study.

Authors' Contributions
Substantial contributions to conception and design of the study: Çetin Altunal, İbrahim Tayfun Şahiner, Serap Yavuzer, Tümay Sadıkoğlu, Mahir Cengiz.
Acquisition of data, or analysis and interpretation of data: Çetin Altunal, İbrahim Tayfun Şahiner, Tümay Sadıkoğlu, Mahir Cengiz.
Drafting the article: Çetin Altunal, İbrahim Tayfun Şahiner, Serap Yavuzer, Mahir Cengiz.
Making critical revisions related to relevant intellectual content of the manuscript: Çetin Altunal, İbrahim Tayfun Şahiner, Serap Yavuzer, Mahir Cengiz.
Supervision: validation and final approval of the version of the article to be published: Çetin Altunal, İbrahim Tayfun Şahiner, Serap Yavuzer, Mahir Cengiz.

ORCID ID
Çetin Altunal: 0000-0002-1037-5194
İbrahim Tayfun Şahiner: 0000-0002-3921-7675
Serap Yavuzer: 0000-0001-7618-9987
Mahir Cengiz: 0000-0003-3343-8650
Tümay Sadikoğlu: 0000-0001-5597-6711

References

1) Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism 2019; 92: 6-10.
2) Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, Aguilar-Salinas CA. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017; 390: 2627-2642.
3) Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir P, Tuomilehto J. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013; 28: 169-180.
4) Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med 2007; 357: 370-379.
5) Golden A. Current pharmacotherapies for obesity: a practical perspective. J Am Assoc Nurse Pract 2017; 29: 43-52.
6) Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes 2005; 29: 1153.
7) Leslie WS, Hankey CR, Lean ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. QJM 2007; 100: 395.
8) Lau DC. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. CMAJ 2007; 176: 1103.
9) Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG. Meta-analysis: surgical treatment of obesity. Ann Intern Med 2005; 142: 547.
10) Busetto L, Segato G, De Luca M, Bortolozzi E, Maccari T, Magon A, Inelmen EM, Favretti F, Enzi G. Preoperative weight loss by intragastric balloon in super-obese patients treated with laparoscopic gastric banding: a case-control study. Obes Surg 2004; 14: 671.
11) Wheeler A, Smith HS. Botulinum toxins: mechanisms of action, antinociception and clinical applications. Toxicology 2013; 306: 124-146.
12) Storr M, Allescher HD, Rösch T, Born P, Weigert N, Classen M. Treatment of symptomatic diffuse esophageal spasm by endoscopic injections of botulinum toxin: A prospective study with long-term follow-up. Gastrointest Endosc 2001; 54: 754-759.
13) Brisinda G, Cadeddu F, Brandara F, Maria G. Management of defecation disorders with botulinum neurotoxin. Aliment Pharmacol Ther 2004; 19: 1131-1133.
14) Elder KA, Wolfe BM. Bariatric surgery: a review of procedures and outcomes. Gastroenterology 2007; 132: 2253.
15) Gui D, Mingrone G, Valenza V, Spada PL, Mutignani M, Runfola M, Scarfone A, Di Mungo M, Panunzi S. Effect of botulinum toxin antral injection on gastric emptying and weight reduction in obese patients: a pilot study. Aliment Pharmacol Ther 2006; 23: 675-680.

16) Foschi D, Corsi F, Lazzaroni M, Sangaletti O, Riva P, La Tartara G, Bevilacqua M, Osio M, Alciati A, Porro GB, Trabucchi E. Treatment of morbid obesity by intraparietogastric administration of botulinum toxin: a randomized, double-blind, controlled study. Int J Obes 2007; 31: 707-712.
17) Albani G, Petroni ML, Mauro A, Liuzzi A, Lezzi G, Verti B, Marzullo P, Cattani L. Safety and efficacy of therapy with botulinum toxin in obesity: a pilot study. J Gastroenterol 2005; 40: 833-835.
18) Sánchez Torralvo FJ, Vázquez Pedreño L, Gonzalo Marín M, Tapia MJ, Lima F, García Fuentes E, García P, Moreno Ruiz J, Rodríguez Cañete A, Valdés S, Olveira G. Endoscopic intragastric injection of botulinum toxin A in obese patients on bariatric surgery waiting lists: A randomised double-blind study. Clin Nutr 2020; 10: 1834-1842.
19) Holst JJ, Deacon CF. Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia 2005; 48: 612-615.
20) Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374: 39-47.
21) Victoza (package insert). Novo Nordisk: Plainsboro, NJ, 2015.
22) Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res 2012; 2012: 672658.
23) Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying long lasting effects on body weight. Diabetes Obes Metab 2012; 14: 531-538.
24) Dossat AM, Diaz R, Gallo L, Panagos A, Kay K, Williams DL. Nucleus accumbens GLP-1 receptors influence meal size and palatability. Am J Physiol Endocrinol Metab 2013; 304: 1314-1320.
25) Zhang P, Liu Y, Ren Y, Bai J, Zhang G, Cui Y. The efficacy and safety of liraglutide in the obese, non-diabetic individuals: a systematic review and meta-analysis. Afr Health Sci 2019; 19: 2591-2599.
26) Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean MEJ, Niskanen L, Rasmussen MF, Rissanen A, Rossner S, Savolainen MJ, Van Gaal L. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes 2012; 36: 843-854.
27) Clemmensen C, Finan B, Fischer K, Tom RZ, Legutko B, Sehrer L, Heine D, Grassl N, Meyer CW, Handerson B, Hofmann SM, Tschop MH, Van Der Ploeg LHT, Muller TD. Dual melanocortin-4 recep- tor and GLP-1 receptor agonism amplifies metabolic benefits in diet- induced obese mice. Embo Mol Med 2015; 7: 288-298.