ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616-056.527:616.12-008.331.1

The impact of intragastric balloon and therapy by glucagon-like peptide-1 receptor agonist on arterial hypertension and other components of metabolic syndrome

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Received 31 August 2015;
accepted 22 March 2016.

Abstract

Objective. Underlying the development of insulin resistance (IR), abdominal obesity (AO) to a large extent determines the occurrence of both type 2 diabetes mellitus (T2DM) and arterial hypertension (HTN). Consequently, obesity treatment has a pathogenetic significance. However, in T2DM there are certain associated difficulties. Feasible methods in this group are the intra-gastric balloon (IGB) implantation and glucagon-like peptide-1 (aGLP-1) receptor agonists. **The aim** of the study was to compare the effects of IGB therapy and aGLP-1 therapy on the various components of metabolic syndrome (including HTN) in T2DM patients. **Design and methods.** The study involved 19 patients, aged from 18 to 65 years old, with obesity (BMI > 35 kg/m^2), T2DM, AO, and HTN. IGB ("MedSil", Russia) was inserted in 10 patients, and subcutaneous injection of GLP-1 (exenatid) was administered to 9 patients. At each visit (0, 2nd, 6th, 12th, and 24th week of research) anthropometric parameters, systolic (SBP) and diastolic blood pressure (DBP), as well as the required number and dosage of hypoglycemic and anti-hypertonic medication were assessed. At baseline and after 24 weeks of treatment, indicators of T2DM compensation were assessed, and HOMA index was calculated. **Results.** After 24 weeks of treatment, there was a decrease in BMI by 5,1 [2.4; 8,1] kg/m^2 ($p < 0.0001$), HbA1c by 1.1 [0.5; 2.0]% ($p = 0.04$), SBP by 17 [7.8; 26.3] mm Hg ($p = 0.003$), DBP by 13.0 [6.5; 19.5] mm Hg ($p = 0.000$) in the IGB group, whereas in the aGLP-1 group BMI decreased by 3.4 [2.7; 4.1] kg/m^2 ($p = 0.000$), HbA1-by 1.0 [0.8; 1.9]% ($p = 0.008$), SBP — by 20 [4.0; 33.0] mm Hg ($p = 0.009$), DBP — by 12.0 [1.5; 16.5] mm Hg ($p = 0.003$). However, the differences between the groups were not significant ($p > 0.05$). **Conclusions.** Both the insertion of IGB and aGLP-1 therapy resulted in a comparable decrease in BMI, HB1C, and BP level in obese patients with T2DM.

Key words: obesity, type 2 diabetes mellitus, arterial hypertension, intragastric balloon, glucagon-like peptide-1 receptor agonist

For citation: Melnikova EV, Babenko AY, Neymark AE. The impact of intragastric balloon and therapy by glucagon-like peptide-1 receptor agonist on arterial hypertension and other components of metabolic syndrome. Arterial'naya Gipertenziya = Arterial Hypertension. 2016;22(2):160–168. ***doi: 10.18705/1607-419X-2016-22-2-160-168.***

Влияние баллонирования желудка и терапии агонистом рецепторов глюкагоноподобного пептида-1 на артериальную гипертензию и другие компоненты метаболического синдрома

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Статья поступила в редакцию 31.08.15 и принята к печати 22.03.16.

Резюме

Актуальность. Абдоминальное ожирение (АО) как основная причина инсулинорезистентности (ИР) в значительной степени детерминирует развитие сахарного диабета 2-го типа (СД2) и артериальной гипертензии (АГ). В связи с этим лечение АО имеет патогенетическое значение. Сложности в решении данной проблемы возникают у больных СД2. Установка внутрижелудочного баллона (ВЖБ) и терапия агонистами рецепторов глюкагоноподобного пептида-1 (аГПП-1) оказывают влияние на патогенетические механизмы развития метаболического синдрома (МС). **Цель работы** — сравнить влияние терапии ВЖБ и аГПП-1 на компоненты МС у больных СД2 и ожирением. **Материалы и методы.** В исследовании участвовали мужчины и женщины в возрасте от 18 до 65 лет с СД2, индексом массы тела (ИМТ) ≥ 35 кг/м^2, АО, АГ. ВЖБ («МедСил», Россия) был установлен 10 пациентам, подкожное введение аГПП-1 (эксенатид) получали 9 человек. На каждом визите (0, 2, 6, 12 и 24 неделя исследования) оценивались антропометрические показатели, ИМТ, уровень систолического (САД) и диастолического артериального давления (ДАД), количество и дозы сахароснижающих и антигипертензивных препаратов. Исходно и через 24 недели оценивались показатели компенсации СД, расчет индекса HOMA. **Результаты.** Через 24 недели лечения в группе ВЖБ получено снижение ИМТ на 5,1 [2,4; 8,1] кг/м^2 (p = 0,000), HbA1c на 1,1 [0,5; 2,0] % (p = 0,04), САД на 17 [7,8; 26,3] мм рт. ст. (p = 0,003), ДАД на 13,0 [6,5; 19,5] мм рт. ст. (p = 0,000), а в группе лечения аГПП-1 уменьшение ИМТ на 3,4 [2,7; 4,1] кг/м^2 (p = 0,000), HbA1c на 1,0 [0,8; 1,9] % (p = 0,008), САД на 20 [4,0; 33,0] мм рт. ст. (p = 0,009), ДАД на 12,0 [1,5; 16,5] мм рт. ст. (p = 0,003), однако статистически значимой разницы между группами не достигнуто (p > 0,05). **Выводы.** В результате установки ВЖБ и терапии аГПП-1 отмечалось сопоставимое снижение массы тела, HbA1 C и уровня артериального давления у пациентов с СД2 и ожирением.

Ключевые слова: ожирение, сахарный диабет 2-го типа, артериальная гипертензия, внутрижелудочный баллон, агонисты рецепторов глюкагоноподобного пептида-1

Для цитирования: Мельникова Е. В., Бабенко А. Ю., Неймарк А. Е. Влияние баллонирования желудка и терапии агонистом рецепторов глюкагоноподобного пептида-1 на артериальную гипертензию и другие компоненты метаболического синдрома. Артериальная гипертензия. 2016;22(2):160–168. ***doi: 10.18705/1607-419X-2016-22-2-160-168.***

Introduction

Arterial hypertension (HTN) is highly common in most of the developed countries being diagnosed in 30–45 % of the adult population. In Russia HTN is found in 40.8 % of residents. HTN is one of typical components of the metabolic syndrome (MS). The following factors play a key role in HTN development in patients with the MS: abdominal obesity (AO), insulin resistance (IR), and adaptive hyperinsulinemia that lead to the development of endothelial dysfunction, activation of the sympathoadrenal and renin-angiotensin systems as well as increase of sodium reabsorption [2]. As a rule, overweight or obesity chronologically precedes HTN [3, 4]. Type 2 diabetes mellitus (DM2) is also closely related to AO and HTN. AO, being the basis of IR, highly determines the development of both DM2 and HTN. Many studies showed mutual exacerbation of DM and HTN. For example, T. W. Gress et all, demonstrated twice higher incidence of DM2 in hypertensive patients than in patients with normal BP level over the period of 6 years of follow-up (26.5 and 12 %, respectively) [5]. V. V. Solomaa et all confirmed that the HTN risk in patients with fasting glycemia ≥ 6.6 mmol/l was 1.71 times higher than in patients with normal fasting glucose ≤ 5.1 mmol/l [6]. In the Framingham study, in patients with DM, HTN was found more often (54 versus 38 % in patients without DM2, $p < 0.001$), and blood pressure (BP) levels were higher. In addition, the synergetic effect of DM and HTN on the development of myocardial fibrosis and nephropathy was found [7]. The increase in risk of comorbid DM2 in patients with HTN, as already mentioned, is determined by the IR syndrome chronology. The reasons for the increase in HTN incidence in patients with hyperglycemia are more complex. HTN is multifactorial and is triggered by the changes in the glucose level such as oxidative stress leading to endothelial dysfunction with the increase of vasoconstrictive factors' production and activation of the renin-angiotensin and sympathetic nervous system.

As a result, AO treatment in case of HTN and DM2 is of importance for the pathogenesis. Today, because of the low effectiveness of life style modification and the lack of effective medications for treatment of obesity, alternative approaches are investigated [8]. This issue is the most challenging in DM2 due to the marked IR and the deficiency in glucagon-like peptide-1 (GLP-1), as recently shown. Safe and minimally invasive treatment methods are intragastric balloon (IGB) placement and treatment with agonists to glucagon-like peptide-1 receptors (GLP-1a). These methods are believed to have a positive effect on the BP as well. For example, GLP-1a acts through an increase in natriuresis, weight loss and reduction of glycemia variability accompanied by the reduction of oxidative stress and its negative impact on endothelial function and, consequently, BP level. Available data confirm this hypothesis. Meta-analysis of 16 studies evaluated the effect of GLP-1a on BP, both exenatide and liraglutide decreased the systolic BP (SBP) and, to lower extent, diastolic BP (DBP) as compared to placebo and other blood glucose lowering medications (insulin glargine, glimepiride, sitagliptin) [9]. As for the effect of IGB on HTN, there are few studies that showed BP decrease, but the authors did not assess the relation between weight loss and BP decrease [10, 17].

However, to our knowledge no study compared these two methods, therefore the **objective** of our work was to compare the effect of intragastric balloon implantation and GLP-1a on different MS components including HTN in patients with DM2.

Design and methods

We enrolled 19 patients (11 women, 8 men) aged 18 years and older, with DM2 and overweight, body mass index (BMI) ≥ 35 kg/m^2 in an open-label comparative randomized prospective study. The following exclusion criteria were applied: uncompensated hypothyroidism, endogenous hyperadrenocorticism, contraindications to IGB placement (inflammatory diseases of the digestive tract, including intractable esophagitis, peptic ulcers, big hiatal hernias, Crohn's disease, malignant tumors of the digestive tract,

esophageal varices of esophagus or stomach, telangiectasias, congenital abnormalities of the digestive tract (atresia, stenosis), throat and esophagus strictures and diverticles, history of stomach and intestine surgeries, severe comorbidities, mental disorders, alcohol and/or drug abuse, allergic response to silicon, pregnancy and lactation) and GLP-1a treatment (hypersensitivity, type 1 DM, diabetic ketoacidosis, history of pancreatitis, severe renal insufficiency (creatinine clearance < 30 ml/min), severe diseases of the digestive tract with accompanying gastroparesis, children under 18 years old). At each scheduled visit (week 0, 2, 6, 12 and 24), anthropometric values, SBP and DBP, quantity and doses of antihypertensive and glucose-lowering medications were assessed. At follow-up, patients with target levels of BP/glycemia were allowed to reduce the dose and/or the quantity of medications with compulsory registration of these changes. At the baseline and after 24 weeks, laboratory tests were carried out to assess the metabolic management of DM and HOMA-index calculation.

Table 1

PATIENT CHARACTERISTICS

Parameter	Group 1 (IGB), n = 10	Group 2 (GLP-1 RAs), n = 9	p
Age, years (Me [25; 75])	54 [48; 61]	52 [48.5; 60]	0.787
BMI, kg/m^2 (Me [25; 75])	44.7 [41; 51.7]	42.1 [39; 51.9]	0.397
WC, cm (Me [25; 75])	139 [132.8; 147]	140 [115.5; 149]	0.427
HC, cm (Me [25; 75])	131.5 [128.3; 144.8]	134 [112.5; 147]	0.507
WC/HC (Me [25; 75])	1.05 [1.0; 1.1]	1.03 [0.96; 1.1]	0.521
WC Female, cm (Me [25; 75])	140 [126.8; 151.8]	140.0 [114.5; 148.0]	0.481
WC Male, cm (Me [25; 75])	138 [134.8; 145]	136.5 [118.3; 154.0]	0.777
HC Female, cm (Me [25; 75])	139 [128.3; 151.5]	145.0 [115.5; 147.0]	0.516
HC Male, cm (Me [25; 75])	130 [121.0; 132.3]	123.0 [111.3; 145.3]	0.905
WC/HC Female (Me [25; 75])	1.03 [0.9; 1.1]	0.97 [0.94; 1.03]	0.428
WC/HC Male (Me [25; 75])	1.09 [1.03; 1.15]	1.08 [1.05; 1.12]	0.840
Fasting plasma glucose, mmol/L (Me [25; 75])	7.8 [6.8; 8.8]	9.5 [7.3; 10.4]	0.049
HbA1c, % (Me [25; 75])	7.8 [6.8; 8.9]	8.4 [8.2; 8.8]	0.474
HOMA-IR (Me [25; 75])	8.8 [3.9; 11.2]	7.3 [4.9; 9.2]	0.902
SBP, mm Hg (Me [25; 75])	140 [132.8; 156.8]	152 [122.5; 158.5]	0.943
DBP, mm Hg (Me [25; 75])	90.5 [85; 102]	93 [79.5; 98]	0.760
Sensitizer (metformin), % (n)	80 (8)	100 (9)	0.474
Secretagog (sulfonylurea drug, DPP4i), % (n)	40 (4)	55.6 (5)	0.656
Insulin, % (n)	40 (4)	22.2 (2)	0.628
RAS inhibitor, % (n)	100 (10)	88.9 (8)	0.474
CA therapy, % (n)	30 (3)	0 (0)	0.211
Diuretics, % (n)	50 (5)	33.3 (3)	0.650
BB, % (n)	30 (3)	66.7 (6)	0.179
Centrally acting agents, % (n)	0 (0)	22.2 (2)	0.211

Note: IGB — intragastric balloon; GLP-1 RAs — glucagon-like peptide-1 receptor agonist; BMI — body mass index; WC — waist circumference; HC — hip circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; HbA1c — glycosylated hemoglobin; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance; SU — sulfonylurea; DPP4i — dipeptidyl peptidase-4 inhibitors; RAS — renin-angiotensin system; CA — calcium antagonists; BB — beta-blockers; p — significant differences between groups.

By the biased-coin approach all patients were randomly assigned to one of 2 study groups. In the first group (n = 10, 4 men, 6 women), an IGB (MedSil, Russia) was inserted with the help of an endoscope. In the second group (n = 9, 4 men, 5 women), a subcutaneous administration of GLP-1a (exenatide in the initial dose 5 μg twice daily, up to 10 μg twice daily after 2 weeks) was added to the glucose-lowering therapy. All patients signed an informed content to take part in the study. The study protocol was approved by the Ethics Committee of the V.A. Almazov Federal North-West Medical Research Centre (protocol No. 63 dated 14.04.2014). The baseline data of both groups are given in Table 1.

All participants had abdominal obesity (AO), HTN, DM2. In the group of GLP-1a treatment, at the baseline, the fasting glucose level was significantly higher (p = 0.049), other parameters including glucose-lowering and anti-hypertensive therapy were comparable in the groups. Obesity was diagnosed based on the BMI value according to the World Health Organization classification (World Health Organization, 2000). BMI was calculated as follows: body weight (kg)/body height (m)^{2}. For the assessment of obesity type, waist circumference (WC) was measured with a measuring tape in the horizontal plane midway between the lower rib margin and the iliac crest on the mid-axillary line. Abdominal type of obesity was diagnosed according to the recommendations of the International Diabetes Federation (International Diabetes Federation, 2006), when WC equaled 94 cm for men and 80 cm for women or more. BP measurement was carried out according to the recommendations of the All-Russian Scientific Society of Cardiology

Table 2

ANTHROPOMETRIC DATA, CARBOHYDRATE METABOLISM, INSULIN RESISTANCE AND BLOOD PRESSURE IN THE STUDY GROUPS

Parameter	Group 1 (IGB), n = 10			Group 2 (GLP-1 RAs), n = 9		
	Baseline	After 24 weeks	p	Baseline	After 24 weeks	p
BMI, kg/m^2 (Me [25; 75])	44.7 [41; 51.7]	39.4 [34.7; 46.9]	0.001	42.1 [39; 51.9]	39.3 [36.3; 48.3]	< 0.001
WC, cm (Me [25; 75])	139 [132.8; 147]	128 [120; 136]	0.001	140 [115.5; 149]	134.0 [108.5; 142.5]	< 0.001
HC, cm (Me [25; 75])	131.5 [128.3; 144.8]	126.5 [116.8; 133]	0.05	134 [112.5; 147]	130.0 [110.5; 142.0]	< 0.001
Fasting plasma glucose, mmol/L (Me [25;75])	7.8 [6.8; 8.8]	6.0 [5.7; 6.4]	0.001	9.5 [7.3; 10.4]	6.2 [5.7; 7.2]	0.005
HbA1c, % (Me [25;75])	7.8 [6.8; 8.9]	6.5 [5.6; 7.1]	0.04	8.4 [8.2; 8.8]	7.4 [5.9; 7.7]	0.008
HOMA-IR (Me [25;75])	8.8 [3.9; 11.2]	4.1 [3.0; 10.5]	0.823	7.3 [4.9; 9.2]	3.3 [2.2; 4.2]	< 0.001
SBP, mm Hg (Me [25; 75])	140 [132.8; 156.8]	130.5 [120.8; 134.3]	0.003	152 [122.5; 158.5]	127.0 [117.5; 132.5]	0.009
DBP, mm Hg (Me [25; 75])	90.5 [85; 102]	80.0 [71.8; 83.3]	0.001	93 [79.5; 98]	80.0 [77.5; 81.5]	0.003

Note: IGB — intragastric balloon; GLP-1 RAs — glucagon-like peptide-1 receptor agonist; BMI — body mass index; WC — waist circumference; HC — hip circumference; HbA1c — glycosylated hemoglobin; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance; SBP — systolic blood pressure; DBP — diastolic blood pressure; p — significant differences before and after treatment.

Table 3

THE DYNAMICS OF ANTHROPOMETRIC DATA, CARBOHYDRATE METABOLISM, BLOOD PRESSURE

Parameter	Group 1 (IGB), n = 10	Group 2 (GLP-1 RAs), n = 9	p_{1-2}
BMI, kg/m^2 (Me [25; 75])	5.1 [2.4; 8.1]	3.4 [2.7; 4.1]	0.084
WC, cm (Me [25; 75])	10 [5.0; 14.3]	7.0 [6.0; 8.5]	0.179
HC, cm (Me [25; 75])	4.5 [2.0; 14.0]	4.0 [2.5; 7.0]	0.245
Fasting plasma glucose, mmol/L(Me [25; 75])	1.6 [1.0; 2.8]	2.2 [0.9; 4.7]	0.371
HbA1c, % (Me [25; 75])	1.1 [0.5; 2.0]	1.0 [0.8; 1.9]	0.838
SBP, mm Hg (Me [25; 75])	17.0 [7.8; 26.3]	20.0 [4.0; 33.0]	0.797
DBP, mm Hg (Me [25; 75])	13.0 [6.5; 19.5]	12.0 [1.5; 16.5]	0.465

Note: IGB — intragastric balloon; GLP-1 RAs — glucagon-like peptide-1 receptor agonist; BMI — body mass index; WC — waist circumference; HC — hip circumference; HbA1c — glycosylated hemoglobin A; SBP — systolic blood pressure; DBP — diastolic blood pressure; Δ — differences compared to baseline value; p1-2 — differences between groups 1 and 2.

(ARSSC, 2013). HbA1c level (%) was determined by means of affinity chromatography on the Bio-Rad D-10 analyzer. Insulin (μIU/l) was assessed by the immunoenzyme assay (ARCHITECT I 1000SR analyzer, Abbott, USA). Fasting plasma glucose (mmol/l) was measured by the glucose oxidase test (Cobas c311 analyzer, Roche, Germany), then insulin resistance index was calculated using the small homeostasis model — HOMA (Homeostasis Model Assessment) suggested by D. R. Matthews et all (1985). The HOMA-IR was calculated as follows: fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5. At each visit, taking into account the BP level and data from the diary of glycemia self-control, titration of antihypertensive and glucose-lowering medications was carried out when necessary. At the end of the study, for the data processing the patients were divided into 2 groups: participants were assigned to the first one if they needed no reduction of the doses and/or quantity of medications after 24 weeks, and patients with reduced doses and/or quantities of medications were assigned to the second one.

Statistical analysis

Statistical analysis was carried out with the program Statistica v.7.0. Descriptive statistics are shown as median and quartiles (25th and 75th percentile). To assess the differences between dependent samples, the non-parametric Wilcoxon test was used. With the help of the Mann–Whitney rank test, the differences of independent variables was determined. Spearman relationship (correlation) analysis was carried out. For the comparison of nominal variables, χ^2 (Fisher's exact test) was used. Differences were considered significant at p-level < 0.05.

Results

All participants completed the study. In both groups no complications were found during the follow-up. After 24 weeks in both groups, BMI, WC and hip circumference reduced (Table 2), but no differences between the groups were found (Table 3).

The carbohydrate metabolism in patients of both groups was assessed by the fasting glycemia and HbA1c. Significant improvement was found in both groups (Table 2), but no considerable differences between the first and the second groups were shown (Table 3).

HOMA index decreased after 24 weeks only in patients receiving GLP-1a (Table 2).

SBP and DBP decreased in both groups by the end of the study (Table 2), without considerable differences between the groups (Table 3). Therefore, the number of antihypertensive therapy after 24 weeks was reduced in 40 % of patients who underwent gastric ballooning

Table 4

THE DYNAMICS OF BLOOD PRESSURE AFTER 24 WEEKS DEPENDING ON THE GRADE OF ARTERIAL HYPERTENSION

Parameter	Group 1 (IGB), n = 10			Group 2 (GLP-1 RAs), n = 9		
	Grade 1 HTN	Grade 2 and 3 HTN	p	Grade 1 HTN	Grade 2 and 3 HTN	p
Δ SBP, mm Hg	10.5 ± 9.0	29.5 ± 13.7	0.028	15.5 ± 13.9	31.0 ± 19.0	0.2
Δ DBP, mm Hg	8.8 ± 6.4	19.8 ± 4.3	0.018	7.2 ± 6.8	17.3 ± 3.2	0.048
Δ SBP, %	7.2 ± 5.8	17.8 ± 6.9	0.031	10.0 ± 9.0	17.7 ± 10.1	0.284
Δ DBP, %	9.5 ± 6.9	18.8 ± 3.5	0.04	7.3 ± 6.9	16.7 ± 2.9	0.025

Note: IGB — intragastric balloon; GLP-1 RAs — glucagon-like peptide-1 receptor agonist; HTN — arterial hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure; Δ — differences compared to baseline value; p — differences before and after treatment.

and in 22.2 % of patients receiving GLP-1a, but the difference was non-significant (p = 0.628). The number and/or doses of glucose-lowering medications were also reduced in 80 % of participants after IGB implantation and in 44.4 % patients receiving GLP-1a. Differences between the groups were non-significant (p = 0.170).

Considering the evidence of more significant BP decrease with GLP-1a treatment in patients with more marked HTN at baseline, we also carried out analysis in subgroups with various HTN severity. Since HTN stage 3 was diagnosed only in one patient in each group, subgroups with HTN stage 2 and 3 were combined. In the gastric ballooning group, more significant decrease of both SBP and DBP was registered in the subgroup with more severe HTN at baseline, unlike GLP-1a group, where in the subgroup with more severe HTN at baseline only DBP decrease was more significant (Table 4).

Correlation analysis of weight loss and HTN showed significant correlations in the gastric ballooning group (for SBP, r = 0.695, p = 0.026; for DBP, r = 0.690, p = 0.027), but not in the group of GLP-1a (for SBP, r = –0.152, p = 0.696; for DBP, r = 0.027, p = 0.945).

Discussion

Our study showed comparable HTN decrease and improvement in other metabolic indices (BMI, WC, HbA1 c) in patients with DM2 and obesity in both GLP-1a treatment and IGB implantation [11–16].

Our findings are consistent with the results of other studies demonstrating considerable BP decrease with GLP-1a treatment in patients with DM2, concomitant HTN and obesity/overweight. One meta-analysis [9] indicated two important features of these medications: firstly, the most significant SBP decrease with GLP-1a treatment is found in patients with the highest baseline BP; secondly, BP decrease occurred well before the weight loss, that is regarded by the authors as an evidence of the leading role of the mechanisms independent of body weight changes, in particular, increase of natriuresis. In our study, more substantial DBP decrease in patients receiving GLP-1a with more severe HTN was also found, and there was no correlation between the weight loss and BP decrease.

According to the available data, gastric ballooning causes both SBP and DBP decrease in obese patients with HTN [10, 17]. We assessed BP changes in patients with DM2, HTN and obesity/overweight and found a comparable to other studies BP decrease. There was a clear association between weight changes and BP in the intervention group. For example, N. Crea et all (2009) found BP decrease associated with the weight loss in IGB treatment group, at 6-month follow-up after the balloon removal weight gain and BP increase were found evidencing

the association between BP reduction and body weight with this treatment approach [18]. Our study showed a positive correlation between body weight changes and BP decrease in IGB group. We assume that various mechanisms of BP reduction develop in IGB and GLP-1a treatment. Taking into account a more significant reduction of antihypertensive and glucose-lowering therapy after IGB implantation, this intervention method may be a preferable treatment option for patients with multi-agent therapy.

A limitation of this study is the small sample, which requires careful interpretation of the results.

Conclusions

IGB implantation and GLP-1a treatment have comparable favourable effects on body weight, glycemic control and BP in patients with DM2, HTN and obesity/overweight. Patients with HTN stage 2 and 3 show more marked SBP reduction. BP changes after IGB implantation correlate clearly with the weight loss, while in the GLP-1a group there was no such correlation.

Conflict of interest

The authors declare no conflict of interest.

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