EFFECTS OF BODY WEIGHT REDUCTION ON ARTERIAL STIFFNESS AND ENDOTHELIAL FUNCTION AFTER BARIATRIC SURGERY IN MORBIDLY OBESE PATIENTS: A 4-YEAR CLINICAL STUDY

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Abstract

Objective. To determine the long-term effect of weight loss on arterial stiffness, metabolic parameters in morbidly obese patients who underwent laparoscopic adjustable gastric banding (LAGB).

Subjects. Forty-eight morbidly obese Caucasian subjects underwent LAGB from January 2009 to January 2010 and completed 4 years follow-up.

Measurements. Patients were evaluated for body mass index (BMI), waist circumference, arterial blood pressure (BP), metabolic factors: leptin, adiponectin, glucose, glycated haemoglobin (HbA1c), insulin. Endothelial function - evaluated as reactive hyperemic index (RHI). Arterial stiffness - determined by cardio - ankle vascular index (CAVI).

Results. Average BMI decreased from 46.48 ± 7.06 kg/m² to 39.78 ± 7.36 kg/m² (1year, $p < 0.001$) and 37.29 ± 7.49 kg/m² (4years, $p = 0.012$). The systolic BP and heart rate reduction were observed after the 4 years. Changes in cardiovascular parameters were accompanied by waist circumference reduction and improvement of glucose metabolism, reduction of insulin, HbA1c, leptin, C-reactive protein values. However, there were statistically significant increases in CAVI 6.58 ± 1.77 m/s vs. 7.03 ± 2.00 m/s ($p = 0.014$) at 1 year, but not significant 7.12 ± 2.19 ($p = 0.153$) after 4 years. Endothelial changes were observed only in diabetic patients one year after LAGB 2.18 ± 0.57 vs. 1.86 ± 0.34 ($p = 0.021$) vs. 2.05 ± 0.42 ($p = 0.086$).

Conclusion. Weight reduction induced by LAGB was associated with changes in body weight and metabolic parameters, but it was no improvement on endothelial function and arterial stiffness.

Key words: bariatric surgery, Arterial Stiffness, endothelial function, laparoscopic adjustable gastric banding operation, Morbid obesity.

INTRODUCTION

Bariatric surgery has been demonstrated to be effective to reduce most obesity-associated risk factors

(1, 2), also reducing morbidity and overall mortality (3-5). Nevertheless, few clinical studies have explicitly examined the relationship between intentional weight loss and cardiovascular mortality. The most convincing data emerged from the Swedish Obese Subjects (SOS) study showing reduced long-term cardiovascular mortality following bariatric surgery, largely owing to decreased myocardial infarction risk (5).

The impact of an overweight or obese status on CVD risk is likely to be due to a number of factors. Weight gain induces both structural and functional changes in perivascular adipose tissue, which is a metabolically active endocrine organ that secretes detrimental adipocytokines such as leptin, resistin, IL-6, IL-17 or TNF- α . Obesity is associated with a low-grade inflammatory status which, in turn, can disrupt adipokines production and secretion, leading to deregulation of adipokines (6), and other important regulatory factors (7). These inflammatory factors are related to endothelial dysfunction and vascular damage by influencing the vascular tone in a paracrine way (8).

In addition, peripheral vascular disease may be caused by hemodynamic changes in obese individuals. Obesity increases cardiac output and circulating volume (9, 10). All these hemodynamic features increase blood pressure which may lead to structural adaptations in the arteries over time. Therefore, methods of assessing endothelial function and arterial stiffness might be predictors of future cardiovascular events, independent of other risk factors of cardiovascular disease (11).

The cornerstone of cardiovascular risk reduction in obese individuals is weight loss. Studies show that blood pressure, fasting glucose level, lipid profile improve with weight reduction in morbidly obese individuals (12). However, the effect of weight loss on endothelial function and arterial stiffness is controversial and depends on multiple factors. A

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dietary weight reduction and exercise intervention has been demonstrated to reduce arterial stiffness (13). Our aim was to evaluate whether long term metabolic changes following weight reduction after the LAGB are converted into a sustainable cardiovascular system improvement.

METHODS

Study Population

Forty-eight morbidly obese patients referred for bariatric surgery were recruited from Vilnius University Hospital Santaros Outpatient Clinic. Patients were included if their body mass index (BMI) was ≥ 35 kg/m² with at least one obesity related comorbidity (such as type II diabetes (T2DM), hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease, or a BMI ≥ 40 kg/m². Previous bariatric surgery, contraindications for laparoscopic operation, pregnancy and patient's refusal were exclusion criteria for study participation. The study protocol was approved by the Lithuanian Bioethics Committee and participants provided informed written consent.

Anthropometric measurements and physical examination

Assessments were obtained at baseline, one year and four years after the LAGB surgery. Height, waist circumference and body weight were measured to the nearest 0.1 cm and 0.1 kg respectively, by using standardized equipment and procedures. Body mass index (BMI) was calculated using the standard formula (weight (kg) / height-squared (m²)).

The excess weight loss (EWL %) was calculated according to the following formula:

$$\text{EWL \%} = \frac{(\text{initial weight} - \text{current weight})}{(\text{initial weight} - \text{ideal weight})} \times 100$$

Body mass analysis was done using Body composition analyzer Jawon Medical Model IOI 353 (Korea) by tetra polar bioelectrical impedance method according to the manufacturer's instructions (14).

Blood pressure (BP) measurements were performed on seated subjects over a 10 min resting period by standard aneroid sphygmomanometer. The mean of the two measurements was recorded.

Blood tests

Fasting blood tests included plasma glucose (Glu), glycated haemoglobin (HbA1c), insulin, leptin

and adiponectin. Laboratory tests were measured using commercially available kits on the auto Analyser at Vilnius University Hospital Santaros Clinic's, Centre of Laboratory Diagnostics. An insulin resistance score (HOMA-IR) was computed with the formula: $\text{HOMA-IR} = [\text{glucose (mmol/L)} \times \text{insulin (\mu U/mL)}] / 22.5$, using fasting values.

Measurements of endothelial function

Coronary endothelial dysfunction, a systemic disorder, represents an early stage of atherosclerosis; reactive hyperemia peripheral arterial tonometry is a technique to assess peripheral microvascular endothelial function (15). It was evaluated as reactive hyperemic index (RHI) and assessed using the EndoPAT 2000 device.

The device records endothelium-mediated changes in the digital pulse waveform known as the PAT (peripheral arterial tone) signal. Measurements were performed according to the manufacturer's instructions. Prior to the study, patients were in supine position for 15 minutes in a quiet, temperature-controlled exam room. The blood pressure cuff was wrapped on the upper arm and fingertip probes were attached to subject's index fingers of each hand. After 5 minutes pre-occlusion period, the blood pressure cuff was inflated to supra-systolic pressure for 5 minutes. After cuff release the RHI was calculated through a computer algorithm. Patients with RHI lower than 1.67 were noted to have endothelial dysfunction (15).

Measurements of arterial stiffness

Arterial stiffness was determined by cardio-ankle vascular index (CAVI). Measurement was done using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan). This device simultaneously records electrocardiogram, phonocardiogram, arterial blood pressures and waveforms of both brachial and ankle arteries. Briefly, blood pressure cuffs were wrapped bilaterally on the upper arms and ankles, electrocardiography electrodes were placed on both wrists and phonocardiogram microphone was placed at the right sternal border. Measurements were performed after a resting period of 10 minutes in supine position. The CAVI was automatically calculated by the following formula: $\text{CAVI} = a \{ (2\rho/\Delta P) \ln (P_s/P_d) \text{PWV}^2 \} + b$; where ρ is blood density, ΔP is the difference between systolic and diastolic blood pressure (BP), P_s is systolic BP, P_d is diastolic BP, PWV is pulse wave velocity and a and b are constants. This equation was derived from

Bramwell – Hill's equation and stiffness parameter β . (16). The average coefficient of CAVI variation is 3.8%. The right, left and mean bilateral CAVI values were used in our study.

Statistical analysis

All statistical analysis was performed using STATISTICA software version 7.0. Numerical data were statistically described in terms of mean values $\pm$ standard deviation ($\pm$ SD) or median, minimum and maximum values when appropriate. Categorical data were summarized as frequencies and percentages. Paired-samples t-test was applied to compare pre-surgery and post-surgery changes within subjects. The analysis of Pearson's correlation was performed to determine the relationship between changes in RHI and mean CAVI and some clinical and biochemical variables. Differences were considered statistically significant at two-tailed $p < 0.05$.

RESULTS

Forty-eight obese subjects were included in

the study. The mean age was 47.38 ± 10.77 years and 32 (66.67%) were female. Compared to the preoperative data, four years after the surgery subjects on average lost 24.92 kg and had a mean BMI reduction of 8.83 kg/m^2 . Subjects achieved a 29.90% EWL at one year and 36.57% EWL at four years after LAGB. The anthropometric and laboratory characteristics of the patients at baseline, one year and four years after surgery, are presented in Table 1.

The subjects demonstrated a significant improvement in metabolic parameters: an increase in adiponectin level and a reduction in CRP levels, leptin, glucose, insulin levels and HbA1c. Although, changes in average diastolic blood pressure did not reach significant differences after one and four years post-surgery, systolic blood pressure was significantly lower at four year follow-up (this was achieved without additional antihypertensive treatment).

At baseline, 1 and 4 years, patients with type 2 diabetes ($N=16$), compared with non-diabetic individuals ($N=32$), had significantly higher levels of fasting plasma glucose, HbA1c and HOMA-IR (Table 4).

Table 1. Characteristics of anthropometric and laboratory assessments

	Baseline (n=48)	After 1 year (n=48)	After 4 years (n=48)
Weight (kg)	133.54 $\pm$ 22.46	114.19 $\pm$ 21.24 p<0.001	108.13 $\pm$ 24.70 p<0.001
BMI (kg/m²)	46.48 $\pm$ 7.06	39.78 $\pm$ 7.36 p<0.001	37.29 $\pm$ 7.49 p<0.001
EWL (%)	-	29.90 $\pm$ 14.76	36.57 $\pm$ 23.91
Waist circumference (cm)	133.50 $\pm$ 16.44	117.61 $\pm$ 17.43 p<0.001	113.61 $\pm$ 17.83 p<0.001
HR (beats/min)	71.83 $\pm$ 10.72	66.29 $\pm$ 9.37 p=0.025	65.56 $\pm$ 10.73 p=0.002
sABP (mmHg)	168.79 $\pm$ 22.13	166.24 $\pm$ 30.89 p=0.416	161.81 $\pm$ 25.46 p=0.039
dABP (mmHg)	101.65 $\pm$ 12.01	99.53 $\pm$ 15.45 p=0.291	97.79 $\pm$ 16.37 p=0.056
Adiponectin ($\mu\text{g/mL}$)	10.42 $\pm$ 7.15	14.41 $\pm$ 7.62 p=0.033	15.54 $\pm$ 9.30 p<0.001
Leptin (ng/mL)	34.54 $\pm$ 16.45	26.89 $\pm$ 16.79 p<0.001	20.71 $\pm$ 17.45 p<0.001
Glu (mmol/L)	6.23 $\pm$ 2.36	5.47 $\pm$ 1.13 p=0.003	5.17 $\pm$ 0.54 p=0.002
Insulin (pmol/L)	171.07 $\pm$ 206.32	85.47 $\pm$ 43.39 p=0.003	64.68 $\pm$ 40.92 p=0.001
HOMA-IR	7.91 $\pm$ 12.65	3.09 $\pm$ 1.84 p=0.010	2.18 $\pm$ 1.55 p=0.004
HbA1c (%)	6.15 $\pm$ 1.01	5.58 $\pm$ 0.57 p<0.001	5.70 $\pm$ 0.55 p<0.001

P value represents assessments comparison with baseline.

n- number of patients; BMI - Body mass index; EWL- excess weight loss; sABP – systolic arterial blood pressure; dABP – diastolic arterial blood pressure; Glu – glucose; HOMA-IR - insulin resistance score; HbA1c - glycated haemoglobin.

Endothelial function and arterial stiffness

At baseline 16.67% (8/48) persons met endothelial dysfunction criteria ($RHI < 1.67$), which did not change at 4 year follow-up. Peripheral arterial tone did not change within 1 and 4 years after the surgery (Table 2). Baseline RHI was lower in diabetic than in non-diabetic patients: 2.18 ± 0.57 vs. 1.86 ± 0.34 ($p = 0.021$) (Table 4). Change in RHI (measure of endothelial function) correlated with change in diastolic blood pressure ($r = 0.435$, $p = 0.023$) and change in adiponectin ($r = 0.546$, $p = 0.007$) (Table 3).

Arterial stiffness increased at 1 year after the bariatric surgery, but it was not significantly different from baseline at 4 year follow-up (Table 2). To evaluate the effect of age on arterial stiffness, patients were divided

into 5 groups: 20-29 years, 30-39 years, 40-49 years, 50-59 years and 60-69 years. One year post surgery, CAVI increased by 0.45 m/s on average. Despite relatively rapid arterial stiffening one year after LAGB, CAVI values decrease in patients under 40 and over 60 years of age after the additional three years. In combined patient group, change in arterial stiffness ($\Delta CAVI$) negatively correlated with changes in leptin and anthropometric indices, such as waist circumference, body weight and BMI, and leptin (Table 3). No significant relationship was identified between CAVI changes and blood pressure or biochemical variables.

When we divided our study group into diabetic ($n = 16$) and non-diabetic subgroups ($n = 32$), we found that both arterial stiffness and endothelial function were

Table 2. Endothelial function and arterial stiffness preoperatively, 1 year and 4 years after LAGB surgery

	Baseline (n=48)	After 1 year (n=48)	After 4 years (n=48)
RHI	2.07 ± 0.51	2.01 ± 0.54 $p = 0.948$	2.05 ± 0.42 $p = 0.086$
Mean CAVI, m/s	6.58 ± 1.77	7.03 ± 2.00 $p = 0.014$	7.12 ± 2.19 $p = 0.153$

P value represents assessments comparison with baseline.

n- number of patients; RHI – reactive hyperemic index; CAVI - cardio – ankle vascular index.

Table 3. Correlations between change in RHI and mean CAVI and some clinical and biochemical variables

	r p (2-tailed) values	ΔRHI	Δ Mean CAVI
Δ Waist circumference	r p (2-tailed)	-0.003 0.987	-0.493 <0.001
Δ Body fat	r p (2-tailed)	0.093 0.651	0.113 0.567
Δ Body weight	r p (2-tailed)	0.009 0.966	-0.340 0.021
Δ BMI	r p (2-tailed)	0.011 0.961	-0.323 0.034
Δ sABP	r p (2-tailed)	0.277 0.162	-0.238 0.103
Δ dABP	r p (2-tailed)	0.435 0.023	-0.148 0.314
Δ CRP	r p (2-tailed)	-0.385 0.128	0.050 0.848
Δ Adiponectin	r p (2-tailed)	0.546 0.007	0.248 0.254
Δ Leptin	r p (2-tailed)	0.072 0.764	-0.308 0.064
Δ Insulin	r p (2-tailed)	0.133 0.516	0.039 0.798
Δ Glucose	r p (2-tailed)	0.071 0.735	-0.011 0.942
Δ HbA1c	r p (2-tailed)	0.008 0.972	-0.120 0.444
Δ HOMA -IR	r p (2-tailed)	0.077 0.719	0.036 0.818

BMI - Body mass index; CRP – C-reactive protein; dABP – diastolic arterial blood pressure; HbA1c - glycated haemoglobin; HOMA-IR- homeostasis model assessment-insulin resistance; sABP – systolic arterial blood pressure.

significantly worse in diabetic subgroup compared with the non-diabetic individuals at baseline and after 1 year follow-up (Table 4). CAVI was significantly higher in patients with diabetes at baseline 5.93 ± 1.59 vs. 7.07 ± 1.92 ($p=0.006$) and one year after 6.25 ± 1.72 vs. 9.08 ± 9.27 ($p=0.029$) (Table 4). After 4 years this significance disappears, suggesting a higher volatility of cardiovascular indices in diabetic patients in a longer follow-up period.

DISCUSSION

Obesity is a disease which often causes different comorbidities, such as dyslipidemia, hypertension, diabetes, and cardiovascular disease. The long term results of different weight loss therapies, such as lifestyle and behavior changes, diet, often are insufficient and bariatric surgery becomes one of the most effective treatment options (3). Some authors suggest that the benefits are maintained even 12 years after the procedure (5). In agreement with these findings, our study participants showed reduction in BMI and waist circumference 1 and 4 years after the LAGB. Taken into consideration the chronic history of obesity, longer observation most probably might reveal more beneficial clinical effects. Bariatric surgery has been shown significant beneficial effects on metabolic syndrome features (17, 18), and on major cardiovascular risk factors (19). Likewise, patients in our study demonstrated favorable changes in blood glucose, insulin, HbA1c, CRP, leptin, adiponectin

levels, heart rate, sABP 4 years after the LAGB.

The obtained results suggest that factors leading to arterial stiffness increment are slowing down in a longer follow-up perspective. Further analysis revealed negative highly significant correlation between changes in the waist circumference and CAVI changes after 4 years follow up compared to basal level ($r=-0.493$; $p<0.001$). In general factors contributing to arterial stiffness increment despite significant anthropometric and biochemical metabolic factors improvement especially at an early post-surgery treatment period are unclear and surprisingly it reflects cardiovascular system deterioration observed in drug treated type 2 diabetes individuals. Three large randomized controlled trials looking at intensive glycemic control have either shown no benefit (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation, ADVANCE (20) and Veterans Affairs Diabetes Trial, VADT) (21) or an increase in all-cause mortality (Action to Control Cardiovascular Risk in Diabetes, ACCORD (22) in type 2 diabetes individuals.

An elevated glucose level can cause different deleterious effects on vessels: a non-enzymatic glycation of matrix proteins with the accumulation of glycation end-products within the arterial wall and subsequent arterial stiffness (23). Contrary to a recent study (24) which showed association between fasting glucose and arterial stiffness in overweight and obese individuals, we did not find any significant positive correlation between fasting glucose and CAVI in both men and women. Conversely, we could not demonstrate

Table 4. Comparison of anthropometric, laboratory, cardiovascular characteristics of study groups before and after laparoscopic adjustable gastric banding

Variable	DM (-) (n=32)			DM (+) (n=16)			P value*		
	Baseline	After 1 year	After 4 years	Baseline	After 1 year	After 4 years	P 0	P 1 y	P 4 y
Body weight, kg	136.53±22.10	117.60±23.49	106.73±24.47	139.62±28.20	121.08±29.94	108.02±28.35	0.540	0.527	0.838
BMI, kg/m ²	46.89±6.94	40.39±7.86	36.68±7.60	48.54±8.00	41.99±9.35	37.73±8.49	0.277	0.374	0.592
Waist circumference, cm	133.48±16.72	117.60±18.08	110.41±20.04	139.96±19.63	123.90±22.25	115.78±20.18	0.080	0.154	0.277
Fasting plasma glucose, mmol/L	5.46±0.89	5.18±0.50	5.03±0.52	7.76±2.89	6.20±1.43	5.49±0.60	<0.001	<0.001	0.001
HbA1c, %	5.73±0.69	5.42±0.46	5.55±0.48	6.95±1.48	5.89±0.68	6.20±1.11	<0.001	<0.001	<0.001
HOMA-IR index	5.13±6.17	2.81±1.60	1.62±1.12	12.83±18.55	3.92±2.63	2.70±1.74	0.003	0.022	0.003
Insulin, mU/L	138.39±133.74	83.29±43.69	58.17±57.86	224.97±243.27	92.24±58.02	76.22±43.06	0.022	0.428	0.186
Leptin, ng/mL	38.58±17.27	27.82±17.60	18.92±15.86	35.95±15.69	27.80±16.86	22.56±18.20	0.488	0.995	0.370
Adiponectin, µg/mL	11.15±7.16	14.78±7.30	20.30±22.59	9.00±6.89	14.20±12.08	11.73±8.06	0.166	0.793	0.070
sABP	169.12±25.27	167.67±32.95	159.44±25.08	170.47±28.60	166.67±28.23	159.44±24.44	0.825	0.872	0.871
dABP	100.94±12.58	101.57±16.60	96.15±15.30	101.10±11.67	97.00±13.08	99.85±16.87	0.955	0.205	0.394
Mean CAVI	5.93±1.59	6.25±1.72	6.83±2.18	7.07±1.92	9.08±9.27	7.78±2.04	0.006	0.029	0.108
RHI, m/s	2.18±0.57	2.07±0.55	2.12±0.54	1.86±0.34	2.04±0.46	2.08±0.50	0.021	0.828	0.747

BMI - Body mass index; CAVI - cardio - ankle vascular index; dABP - diastolic arterial blood pressure; EWL- excess weight loss; Glu - glucose; HbA1c - glycated haemoglobin; HOMA-IR - insulin resistance score; RHI - reactive hyperemic index; sABP - systolic arterial blood pressure; n- number of patients.

* P-value compares the readings between diabetic and non-diabetic patients at given time point.

any correlation between CAVI and HOMA-IR as shown in the recent study (24).

In our study, despite improved metabolic parameters, one year after the surgery, arterial stiffness (CAVI) significantly increased ($p=0.014$). Comparing diabetic and non-diabetic persons, CAVI was significantly higher in diabetics at baseline and after 1 year ($p=0.029$). Contrary to a recent study (24), CAVI correlated inversely with reduction in weight, waist circumference and BMI.

There was no statistically significant change in RHI, however when we divided participants into diabetic and non-diabetic, we found that RHI at the beginning was lower in diabetic persons 2.18 ± 0.57 vs. 1.86 ± 0.34 ($p=0.021$). However, one and four years after the LAGB, there were no differences in RHI between the two groups.

The results of this study provide further credence that BMI alone is an inadequate marker of obesity-related cardiovascular risk. The existence of a paradoxical relationship between obesity and cardiovascular health sheds light on severe obesity impact on vascular function. It also raises questions regarding the pleiotropic role of the adipocytes. Relatively preserved vascular function and a positive association with leptin and adiponectin levels were reported previously in subjects with more severe obesity (9). It is also known that adipocytes are a source of endothelial progenitor cells (5). Possibly these cells in some conditions may show a protective and reparative vascular effect and in case of significant fat mass, an excess of progenitor cells are produced, perhaps via stimulation by the chronic inflammatory environment.

It is very important to answer the question of the effect of bariatric surgery on cardiac stiffness and endothelial function.

Weight loss is the first line advice for obese cardiac patients with the aim to improve quality of life and reduce their cardiovascular risk factors. Studies suggest that bariatric surgery in morbidly obese patients can significantly diminish cardiovascular risk factors followed by beneficial cardiovascular outcome (10).

In conclusion, our data provides additional data regarding different endothelial function scenarios in obese individuals suggesting that there might be an early time window during weight loss when cardiovascular risk may actually increase, suggesting that more intensive monitoring is needed during this time.

Conflict of interest

The authors state no conflict of interest.

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