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ORIGINAL ARTICLE

Cardiac and Metabolic Effects of Bariatric Surgery Among Obese Patients in a Malaysian Tertiary Hospital: A 6-month Prospective Cohort Study

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Abstract

Objective. Obesity is known to be associated with left ventricular diastolic dysfunction due to its effect on blood pressure and glucose tolerance. We aimed to investigate whether weight loss after bariatric surgery might improve diastolic dysfunction through in-depth echocardiographic examination.

Methodology. We recruited twenty-eight patients who were about to undergo bariatric surgery by purposive sampling. They underwent echocardiography at baseline and 6 months after surgery with a focus on diastolic function measurements and global longitudinal strain (GLS). They also had fasting serum lipid and glucose measurements pre- and post-surgery.

Results. The mean weight loss after surgery was 24.1 kg. Out of the 28 subjects, fifteen (54%) initially had diastolic dysfunction before surgery. Only two had persistent diastolic dysfunction 6 months after surgery. The mean indexed left atrial volume 6 months post-surgery was 27.1 from 32 ml/m^2 prior to surgery. The average E/e' is 11.78 post-surgery from 13.43 pre-surgery. The left ventricular GLS became (-)25.7% after surgery from (-)21.2% prior to surgery. Their post-surgery fasting serum lipid and glucose levels also showed significant improvement.

Conclusion. Our study reinforced the existing evidence that bariatric surgery significantly improved echocardiographic parameters of diastolic function and left ventricular global longitudinal strain, along with various metabolic profiles.

Key words: bariatric surgery, obesity, diastolic function, GLS

INTRODUCTION

Obesity is defined as body mass index (BMI) more than 30 kg/m^2 by World Health Organization and BMI >27.5 kg/m^2 by the Malaysian clinical practice guidelines (CPG) 2004. Malaysia was declared as the most obese country in Asia in 2014. Half of the population is obese. Obesity has been identified as a significant health issue worldwide. It is associated with detrimental effects on the cardiovascular system leading to morbidity and mortality.[1] In general, obesity is an independent risk predictor for heart failure.[2] It is closely related to cardiovascular risk factors such as hypertension, type 2 diabetes mellitus, and dyslipidemia, which directly affects cardiac structure and function. Excess body fat increases preload and afterload due to hyperdynamic circulation, chronic volume overload, and an increase in peripheral resistance.[3,4] The long-term care of obesity can be debilitating for both the patient and healthcare practitioner. The first bariatric surgery in 1954 by Dr A.J. Kremens was a jejunoileal bypass, which was later altered in 1964 by adding a jejuno-colic shunt. Several types of bariatric surgery methods were introduced throughout the years, with the latest being Roux-en-Y bypass and sleeve gastrectomy. Bariatric surgery is still the most effective weight loss intervention with more persistent benefits.[5]

Dyslipidemia plays a major role in the progression of cardiovascular disease in obesity. It is defined as an elevation in fasting blood total cholesterol, which may or may not be associated with elevated blood triglycerides (TG).[6] Dyslipidemia is further classified by the National Cholesterol Education Program (NCEP) into subtypes of lipoproteins, namely Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and Triglycerides (TG).[7] In a retrospective study among patients who underwent Roux-en-Y gastric bypass, serum total cholesterol, TG, and LDL levels improved in all patients within 6 months after surgery leading to the discontinuation of their lipid-

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lowering agents. HDL level had a slower improvement, reaching the desired target within 12 months after surgery.[8]

Left ventricular (LV) diastolic dysfunction is also commonly associated with obesity. A condition that reflects an impairment in the filling properties of the LV, diastolic dysfunction has been demonstrated to predict future progression to heart failure.[9-11] Diastolic dysfunction refers to the inability of the heart chamber to properly fill with blood during the diastolic phase of the cardiac cycle. This is caused by inadequate relaxation of the ventricles during diastole by both active and passive processes occurring at the level of the myocyte, extracellular matrix, and left ventricular chamber. With regards to the obese population, it was postulated that the negative effects of visceral fat on diastolic function can be accounted for by concentric LV remodeling, elevated myocardial triglyceride levels, and impaired metabolism.[12]

There have been few studies on the effect of bariatric surgery on diastolic dysfunction. A study by Kurnicka et al., looked at the improvement of left ventricular diastolic function and morphology in young women with morbid obesity six months after bariatric surgery. Echocardiography was performed pre and post-surgery. Among the parameters assessed were mitral peak early (E) and atrial (A) velocities, E-deceleration time (DcT), pulmonary vein S, D and A reversal velocities, peak early diastolic mitral annular velocities (E’) and E/E’. The study showed a significant reduction in LV wall thickness and LV mass (mean 183.7 to 171.5 g, $p = 0.001$).[13]

In the Asian population, diastolic dysfunction is detected at a lower BMI level, as compared to Caucasians.[14-21] This was seen in the study by Onzo et al., in 2020 which looked at the impact of ethnicity on cardiac adaptation. The study revealed that body size, left ventricular mass, wall thickness, trabeculation, genotype, and phenotype played a role in deciding one’s cardiac morphology.[22]

Global longitudinal strain (GLS) is an emerging echocardiographic parameter that may predict cardiovascular outcomes and subclinical heart failure. Among the three main strains (longitudinal, radial and rotational), longitudinal strain is more commonly assessed as it is the first to be affected compared to the other strains. However, recent reports showed that the reduction of GLS is independent of heart failure and ejection fraction.[23] Multiple studies have shown improvements in GLS post-bariatric surgery. In a study done by Frea et al., in 2020 involving 40 patients who underwent bariatric surgery, there was an improvement in GLS 10 months after surgery.[24]

In 2019, a meta-analysis of 7 randomized controlled trials examining the outcome of bariatric surgery versus medical treatment for type 2 diabetes mellitus showed that bariatric surgery is superior and has a more persistent effect on type 2 diabetes mellitus remission compared to medical management.[25]

There has not been a comprehensive study looking into the diastolic parameters among patients who underwent bariatric surgery. Hence, we aimed to assess the echocardiographic parameters of diastolic dysfunction, together with blood lipid and glucose levels pre- and post-bariatric surgery, thus giving us an overview of the long-term outcome of bariatric surgery in Malaysia.

METHODOLOGY

Study design and participants

We performed a prospective observational study from January 2022 to August 2022, recruiting patients from the surgical and cardiology clinics at our center before they underwent bariatric surgery. Subjects were recruited by purposive sampling. We included patients with ages between 18 and 50 years old, BMI more than 27.5 kg/m^2, and who were about to undergo either a Roux-en-Y or sleeve gastrectomy. Patients were excluded if they had pre-existing ischemic heart disease, chronic kidney disease (CKD), end-stage renal failure (ESRF), congestive heart failure, atrial fibrillation, valvular heart disease and poor echo window for analysis. They were also excluded if there were regional wall motion abnormalities on their baseline echocardiogram, congenital heart disease, left bundle branch block (LBBB), LVEF of less than 35%, and obvious LVH with LV wall thickness of more than 1.3 cm in the initial echo. For this study, Valsalva maneuver was not done.

Laboratory measurements

The laboratory tests were done at the Department of Pathology of our institution. Fasting serum lipids, fasting blood sugar (FBS), and HbA1c were taken before and 6 months after surgery.

Sample size

We used a one-proportion cross-sectional sample size method, in which the proportion of the studied population is about 1%, based on the expected prevalence of cardiac dysfunction among obese patients 6 months after bariatric surgery, in which a meta-analysis by Veldhuisen et al., showed an incidence between 0.4 to 9.9%[26].

$$N = \frac{Z^2_{\alpha/2} * p * (1 - p) * DEFF}{d^2} \quad b$$

α = probability of type I error = 0.05
p = prevalence proportion = 0.01
DEFF = estimated Effect Size (Usually 1-4) = 1
d = desired level of absolute precision = 0.05
N = Required sample size

The calculated minimum number of sample size is sixteen. Assuming an attrition rate of at least 40%, we recruited a total of 28 patients.

Echocardiographic data

The echocardiographic study was done by a single qualified and certified operator using an ultrasound machine Epic 7C (Philips Ultrasound, Netherlands) system equipped with a 1.6-3.2 MHz phased-array transducer. All the subjects underwent echocardiography prior to and six months after bariatric surgery. The echo parameters used to determine diastolic dysfunction are Left Atrial Volume Index (LAVI) <25 ml/m^2, Average E/e'>14, Septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, TR velocity >2.8 m/s. E wave, E/A and LV strain percentage assessments are also part of the diastolic dysfunction assessment. If less than 50% of the above criteria are met, the diastolic function is considered normal. Diastolic dysfunction is deemed indeterminate if 50% of the above criteria are met. Diastolic dysfunction is regarded as abnormal if more than 50% of the above criteria are met. Grading for diastolic dysfunction was also determined pre-surgery. The algorithm to determine the grading of diastolic dysfunction is based from the American Society of Echocardiography April 2019.

Ethics statement

This study protocol was reviewed and approved by our institutional review board for ethics. Written consent was obtained from all patients involved in the study prior to their participation. All patients were counselled on the risks and benefits of their involvement in the study.

Statistical analysis

Categorical variables were described by frequency and percentage. Continuous variables were described using mean and standard deviation for normally distributed variables. The median and interquartile range (IQR) were reported if the distribution was not normal. Descriptive statistics, such as minimum and maximum values, were reported when necessary. Normality of the data was examined using a histogram (approximately bell-shaped), skewness (within -1 to 1), and kurtosis (within -3 to 3).

For normally distributed datasets, paired t-test was used to compare the differences in the measurements before and after the surgery. Wilcoxon signed-rank test was applied if the distribution of the differences was skewed. A p-value less than 0.05 is considered statistically significant.

McNemar test was used to compare the proportion of diastolic dysfunction before and after bariatric surgery. A p-value less than 0.05 was considered statistically significant. All analyses were performed using SPSS (IBM Corp. Released 2013 IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Table 1. Distribution of subjects according to demographic and clinical characteristics, n = 28

Variables	Overall
Participants (N,%)	28
Gender (N,%)	
Male	8 (29)
Female	20 (71)
Ethnicity (N,%)	
Malay	26 (92)
Chinese	1 (4)
Indian	1 (4)
Hypertension (N,%)	
Yes	13 (46)
No	15 (54)
Diabetes (N,%)	
Yes	9 (32)
No	19 (68)
Dyslipidemia (N,%)	
Yes	15 (54)
No	13 (46)
Types of Surgery	
Roux-en-Y	9 (32)
Sleeve gastrectomy	19 (68)

* Categorical data present as frequency (percentage).

RESULTS

Out of fifty-two patients initially screened, 28 patients met the inclusion and exclusion criteria. All patients completed the study follow-up.

Eight (29%) subjects were males and 20 (71%) were females. Thirteen (46%) have hypertension, 9 (32%) have diabetes mellitus, and 15 (54%) have dyslipidemia (Table 1).

All patients had significant weight loss after surgery as shown in Table 2 and Figure 1. The mean BMI was 44.2 kg/m^2 pre-surgery and 35.6 kg/m^2 post-surgery, with a mean difference of 8.6 kg/m^2 (7.08 – 10.09). The mean systolic blood pressure (SBP) was 141 mm Hg pre-surgery and 121 mmHg post-surgery. There was a significant reduction in SBP with a mean difference of 19.8 mmHg (11.4 – 28.2).

For fasting serum lipid and glycemic control, the results showed statistically significant reductions, as seen in Table 2 and Figures 2 and 3.

For the echocardiographic measurements, there was a statistically significant improvement in all the parameters among the subjects with diastolic dysfunction at baseline as shown in Table 3 and Figure 4.

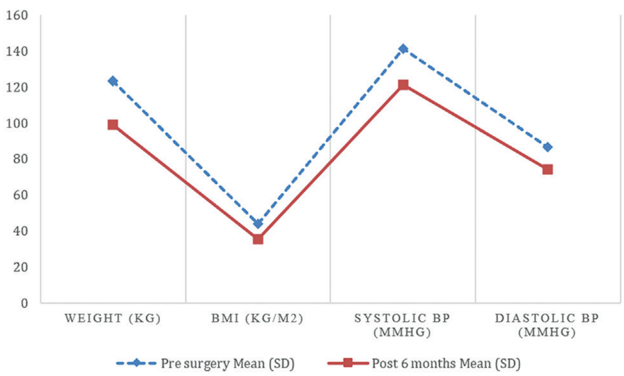

Figure 1. Graph showing comparison between anthropometric and blood pressure parameters before and after bariatric surgery.

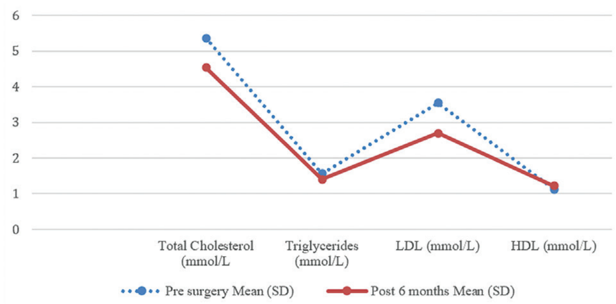

Figure 2. Graph showing comparison of lipid profile before and after bariatric surgery.

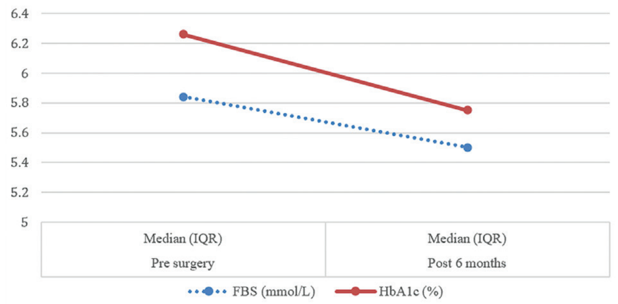

Figure 3. Graph showing comparison of glycemic index before and after bariatric surgery.

Table 2. Pre- and post-surgery results for anthropometric data, fasting lipid profile and glycemic metrics

Variables	Pre-surgery, N = 28	Post-surgery 6 months, N = 28	Mean difference	*p**
Weight in kg (SD)	123.4 (20.2)	99.3 (14.0)	24.1 (19.8 - 28.5)	<0.001
BMI in kg/m^2 (SD)	44.19 (7.29)	35.61 (5.50)	8.59 (7.08 - 10.09)	<0.001
Systolic BP in mmHg (SD)	141.2 (21.3)	121.4 (6.8)	19.8 (11.4 to 28.2)	<0.001
Diastolic BP in mmHg (SD)	86.6 (10.5)	74.4 (6.0)	12.2 (8.7 to 15.7)	< 0.001
Total Cholesterol in mmol/L (SD)	5.36 (1.15)	4.53 (0.76)	0.83 (0.51 to 1.16)	<0.001
Triglycerides in mmol/L (SD)	1.57 (0.59)	1.40 (0.34)	0.17 (0.04 to 0.31)	<0.001
LDL in mmol/L (SD)	3.55 (1.03)	2.70 (0.78)	0.85 (0.55 to 1.16)	<0.001
HDL in mmol/L (SD)	1.12 (0.2)	1.22 (0.16)	-0.09 (-0.16 to -0.03)	0.009
FBS in mmol/L (range)	5.84 (4.87-7.42)	5.50 (5.10-6.56)		0.119**
HbA1c in % (range)	6.26 (5.8-8.13)	5.75 (5.4-7.0)		0.001**
HbA1c in % (range) among subjects with diabetes, n = 9	7.7 (6.03-10.48)	6.70 (5.55-7.68)		0.009**
HbA1c in % (range) among subjects without diabetes, n = 19	5.80 (5.40-6.28)	5.5 (5.40-5.78)		0.018**
LDL in mmol/L (SD) among subjects with dyslipidemia, n = 15	3.67 (0.85)	3.00 (0.62)	0.54 (0.18-0.87)	<0.001
LDL in mmol/ (SD) among subjects without dyslipidemia, N = 13	3.41 (1.22)	2.35 (0.81)	1.05 (0.55-1.58)	0.002

Table 3. Distribution of subjects according to echocardiographic data before and after surgery

Variables	Pre-surgery (all patients), N = 28	Post-surgery 6 mos (all patients), N = 28	p *	Pre-surgery with normal DF, N = 13	Post-surgery 6 mos with normal DF, N = 13	Mean difference	Pre-surgery with abnormal DF, N = 15	Post-surgery 6 mos with abnormal DF, N = 15	Mean difference	*p**	Mean difference pre and post LSG, N = 19	Mean difference pre and post ReY	*p**
LAVI in ml/m^2 (range)	32.0 (27.3 - 36.0)	27.1 (25.0 - 33.0)	<0.001**	28 (25.6-31.5)	25 (24.5-28.05)	2.0 (0.6-2.2)	36 (33-42)	33 (27-34)	3.2 (2.0-8.9)	0.01**	2.00 (1-7)	3.0 (1.5-5.45)	0.905
Average E/e' (SD)	13.43 (2.71)	11.78 (2.48)	0.001	11.61 (2.29)	10.84 (2.51)	0.78 (-0.1-2.11)	14.93 (2.04)	12.36 (2.09)	2.57 (1.5-3.8)	0.04	1.19 (1.76)	2.73 (3.00)	0.105
Septal e' in cm/s (SD)	8.33 (1.70)	9.43 (1.59)	<0.001	9.25 (1.73)	10.06 (1.81)	0.046 (-1.32-1.73)	7.64 (1.19)	8.96 (1.15)	1.33 (-1.91-(-0.85))	0.137	-0.36 (2.5)	-1.4 (1.37)	0.263
Lateral e' in cm/s (SD)	11.37 (2.43)	12.03 (1.90)	0.002	13.21 (1.69)	13.32 (1.56)	-0.115 (-0.59 - 0.33)	9.99 (1.61)	11.06 (1.31)	-1.06 (-1.56 - -0.6)	0.009	-0.56 (0.89)	11.06 (1.31)	0.706
TR Vmax in m/s (SD)	2.53 (0.51)	2.36 (0.29)	0.012	2.20 (0.37)	2.23 (0.25)	-0.03 (-0.15 - 0.09)	2.84 (0.45)	2.49 (0.28)	0.34 (0.17-0.52)	0.003	2.84 (0.45)	-0.71 (1.19)	0.551
LV strain I in % (SD)	-21.2 (3.8)	-25.7 (3.8)	<0.001	-22.9 (3.33)	-26.84 (3.21)	3.85 (2.2-5.56)	-19.79 (3.77)	-25 (3.21)	5.21 (3.64-6.67)	0.24	0.13 (0.32)	0.22 (0.41)	0.79
LVEF in % (SD)	67.7 (7.6)	67.3 (5.3)	0.663	66.76 (6.16)	67.53 (3.54)	-0.77 (-3.0-1.64)	69.14 (8.79)	67.57 (6.49)	1.57 (-1.77-4.35)	0.255	-0.22 (4.77)	1.77 (6.18)	0.361
E wave in cm/s (SD)	59.2 (10.3)	66.6 (13.9)	0.001	64.39 (9.79)	71.62 (13.55)	-7.0 (-11.73 - -3.27)	55.5 (8.44)	63.07 (13.27)	-7.57 (-15.14 - -1.5)	0.907	-8.49 (10.49)	-5.0 (11.66)	0.439
E:A (SD)	1.08 (0.24)	1.17 (0.25)	0.060	1.11 (0.19)	1.14 (0.21)	-0.03 (-0.127 - 0.08)	1.07 (0.27)	1.23 (0.27)	-0.15 (-0.32 - 0.0017)	0.206	-0.07 (0.24)	-0.14 (0.28)	0.46

Abbreviations: LAVI=Left atrial volume index, TR=Tricuspid regurgitation, LVEF=Left ventricular ejection fraction
*Paired t-test; **Wilcoxon signed-rank test. Mean difference (MD) with 95% confidence interval was calculated for paired t-test.

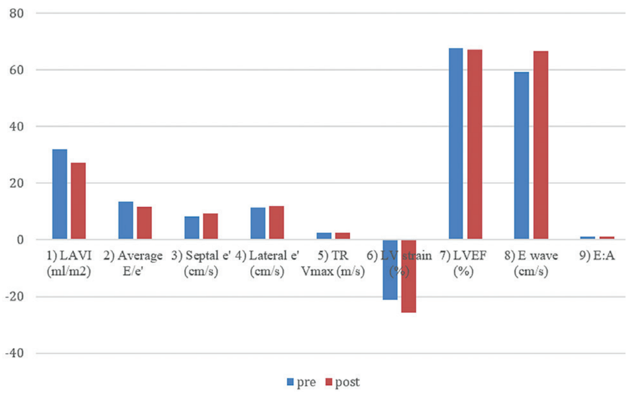

Figure 4. Graph showing comparison of echocardiographic parameters pre- and post-bariatric surgery.

Table 4. Changes in the grade of diastolic dysfunction post bariatric surgery

Grade (N,%)	Pre-surgery, N = 28	Post-surgery, N = 28	*p**
I	4 (14)	2 (7)	
II	7 (25)	0	
Indeterminate	4 (14)	0	
All	15 (54)	2 (7)	<0.05

Out of the 28 patients, 13 (46%) had normal diastolic function, while 15 (54%) had diastolic dysfunction at baseline. The distribution of the grading of their diastolic dysfunction were as follows: grade 1 (4 patients), grade 2 (7 patients) or indeterminate (4 patients). Post-bariatric surgery, echocardiographic data revealed that 26 (93%) had reverted to normal diastolic function while 2 (7%) remained to have diastolic dysfunction, as shown in Table 4.

Subgroup analysis on the effects of bariatric surgery on patients with pre-existing comorbidities

Among patients with and without diabetes, bariatric surgery improved HbA1c levels significantly, as seen in Table 2. Their LDL levels were likewise significantly reduced.

Subgroup analysis on the types of surgery on echocardiographic, glycemic and lipid profile

Nineteen patients (68%) underwent laparoscopic sleeve gastrectomy while nine (32%) underwent mini-gastric bypass with Roux-en-Y technique. The echocardiographic parameters, glycemic and lipid profiles were not significantly different between the two techniques as shown in Table 3.

Subgroup analysis on echocardiographic parameters between patients with normal diastolic function and established diastolic dysfunction

Thirteen (46%) patients had normal diastolic function at baseline while fifteen (54%) patients had diastolic dysfunction. Patients with pre-existing diastolic dysfunction had higher statistical improvements in terms of LAVI, average E/e', lateral e', and TR Vmax post-surgery.

DISCUSSION

Obesity is strongly associated with co-morbidities such as diabetes, hypertension, dyslipidemia and cardiovascular disease[27] which was seen in our study. As previously described, bariatric surgery has led to reductions in weight and associated illnesses.[28] Based on the results presented, there was a significant improvement in the left ventricular diastolic dysfunction after bariatric surgery. Our study also showed that patients with established diastolic dysfunction had improvements in their diastolic parameters (Table 5).

A literature review published in 2017 by Kindel et al., looked at bariatric surgery as one of the modalities to treat heart failure. The review showed that bariatric surgery reduced the risk of heart failure development and reversed abnormalities in cardiac mass, workload, and metabolism with improved diastolic function, potentially enhancing native cardiac systolic function.[29] An American Society of Echocardiography study in 2020 which looked at the impact of bariatric surgery on the echocardiographic features of cardiac remodeling and diastolic function concurred with our findings: patients with pre-existing diastolic dysfunction demonstrated improvements in diastolic function, driven by changes in TR velocity and medial E/e'.[30]

The advent of strain imaging echocardiography now offers a readily available and portable imaging tool that not only offers an objective characterization of myocardial dynamics but also allows for early detection of subclinical left ventricular dysfunction. Multiple studies have shown a direct correlation between obesity and GLS pattern.[31]

Table 5. Pre- and post-surgery results for anthropometric data, fasting lipid profile and glycemic metrics based on the type of surgery

Variables	Pre LSG, N = 19	Post LSG, N = 19	Mean difference	Pre ReY, N = 9	Post ReY, N = 9	Mean difference	*p**
Weight in kg (SD)	120 (18.91)	97.48 (15.54)	22.5 (18.94-27.14)	130.67 (22.05)	103.22 (9.77)	27.44 (18.26-37.09)	0.288
BMI in kg/m² (SD)	42.81 (6.35)	34.80 (5.57)	8.01 (6.73-9.43)	47.12 (8.61)	37.32 (5.23)	9.8 (6.45-13.17)	0.262
Systolic BP in mmHg (SD)	142.3 (22.45)	123 (6.94)	5.62 (5.14-6.03)	138.78 (19.72)	117.89 (5.44)	4.81 (3.97-5.7)	0.079
Diastolic BP in mmHg (SD)	85.94 (9.22)	73.21 (5.47)	12.74 (9.07-16.66)	88 (13.41)	77 (6.67)	11 (4.72-18.5)	0.676
LDL in mmol/L (SD)	3.77 (0.92)	2.89 (0.67)	0.78 (0.42-1.25)	3.08 (1.14)	2.3 (0.87)	0.78 (0.29-1.2)	0.985**
HbA1c in % (range)	6.22 (5.8-7.9)	5.7 (5.4-6.4)		6.7 (5.75-8.26)	6.1 (5.38-7.7)		0.594**

Abbreviations: SD = standard deviation, CI = confidence interval, BP = blood pressure, cm = centimeter, kg = kilogram, mmHg = millimeter mercury, LSG = Laparoscopic Sleeve Gastrectomy, ReY = Roux-en-Y gastric bypass
Data were expressed as mean (standard deviation) for normal distributions and median (first quartile-third quartile) for skewed distributions.
*Paired t-test; **Wilcoxon signed-rank test. Mean difference (MD) with 95% confidence interval was calculated for Paired t-test.

Our study showed that there was a statistically significant change in GLS pre and post-bariatric surgery. Similar to our findings, a prospective study by Lisa et al., showed that the LV longitudinal function largely recovered one year after bariatric surgery due to reduced afterload.[32]

In terms of the metabolic parameters, the lipid profiles of all the subjects significantly improved post-surgery. This was similar to the findings in a meta-analysis by Heffron et al., which looked at the changes in blood lipid levels of 47,779 subjects prior to and one year after bariatric surgery. Regardless of the surgery types (Roux-en-Y or sleeve gastrectomy), our study showed significant improvements in TC, TG, LDL and HDL.[33,34] We also observed an improvement in their glycemic control, with the HbA1c levels significantly decreased six months post-surgery. A finding also seen in a study done in Saudi Arabia by Ahmed et al.[35]

In summary, this study proves the benefit of bariatric surgery for patients with obesity, through the improvement of cardiac function and metabolic parameters. Although largely considered as a treatment of last resort for obesity, bariatric surgery may be a viable option in selected patients at high risk of developing cardiovascular events.

Limitations

The COVID-19 pandemic affected the recruitment of patients as many refused to participate. This is due to the risk of in-hospital infection, as our hospital is a COVID-19 treatment center. Another limitation is that we were unable to fully analyze the baseline echocardiograph results due to poor echo window and inadequate images saved on file.

CONCLUSION

Our study showed significant improvements in the lipid profile, glycemic control, and echocardiographic diastolic function parameters after bariatric surgery.

We also noted a significant improvement in the subjects' GLS parameters which warrants further studies in strain imaging.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MHR: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft preparation; **MAR:** Software, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **SFM:** Validation, Resources, Supervision; **NRKNM:** Validation, Resources, Supervision; **HHCH:** Validation, Supervision, Project administration, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

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